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COVER SHEET FOR PROVISIONAL APPLICATION FOR PATENT

Commissioner for Patents
P.O. Box 1450
Mail Stop Provisional Patent Application
Alexandria, VA 22313-1450

Sir:

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

Docket Number	11134-035-888			Type a plus sign (+) inside this box -	+ +
INVENTOR(S) / APPLICANT(S)					
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)		
[11134-035-888]					
TITLE OF THE INVENTION (280 characters max)					
GPR40 MODULATORS AND METHODS FOR THEIR USE					
JONES DAY CORRESPONDENCE ADDRESS :20583					
ENCLOSED APPLICATION PARTS (check all that apply)					
X ² Specification	Number of Pages	115	<input type="checkbox"/> Applicant claims small entity status, see 37 CFR §1.27 <input type="checkbox"/> Other (specify)		
	X ² Drawing(s)	Number of Sheets	1		
METHOD OF PAYMENT (check one)					
<input type="checkbox"/> A check or money order is enclosed to cover the Provisional filing fees.				ESTIMATED PROVISIONAL FILING FEE AMOUNT <input checked="" type="checkbox"/> \$160 <input type="checkbox"/> \$80	
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge the required filing fee to Deposit Account Number 16-1150.					

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

 No. Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

Signature Roger C. Rich REGISTRATION NO.
 Roger C. Rich for *(if appropriate)*
 JONES DAY Anthony Insogna, Reg. No. 35,203

54,398

Date

2/27/04

 Additional inventors are being named on separately numbered sheets attached hereto.Total number of cover sheet pages. 1**PROVISIONAL APPLICATION FILING ONLY**

GPR40 MODULATORS AND METHODS FOR THEIR USE

1. FIELD OF THE INVENTION

[0001] The present invention relates to compounds capable of modulating the G-protein-coupled receptor GPR40, compositions comprising the compounds, and methods for their use for controlling insulin levels *in vivo* and for the treatment of condition such as type II diabetes, obesity, glucose intolerance, and hypercholesterolemia and related disorders associated with abnormally high or low plasma lipoprotein or triglyceride levels.

2. BACKGROUND OF THE INVENTION

[0002] The production of insulin is central to the regulation of carbohydrate and lipid metabolism. Insulin imbalances lead to conditions such as type-2 diabetes mellitus, a serious metabolic disease that afflicts around 5% of the population in Western Societies and over 150 million people worldwide. Insulin is secreted from pancreatic β cells in response to elevated plasma glucose which is augmented by the presence of fatty acids. The recent recognition of the function for the G-protein coupled receptor GPR40 in modulating insulin secretion has provided insight into regulation of carbohydrate and lipid metabolism in vertebrates, and further provided targets for the development of therapeutic agents for disorders such as obesity, diabetes, cardiovascular disease and dyslipidemia.

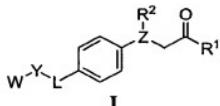
[0003] GPR40 is a member of the gene superfamily of G-protein coupled receptors ("GPCRs"). GPCRs are membrane proteins characterized as having seven putative transmembrane domains that respond to a variety of molecules by activating intra-cellular signaling pathways critical to a diversity of physiological functions. GPR40 was first identified as an orphan receptor (*i.e.*, a receptor without a known ligand) from a human genomic DNA fragment. Sawzdargo *et al.* (1997) *Biochem. Biophys. Res. Commun.* 239: 543-547. GPR40 is highly expressed in pancreatic β cells and insulin-secreting cell lines. GPR40 activation is linked to modulation of the G_q family of intra-cellular signaling proteins and concomitant induction of elevated calcium levels. It has been recognized that fatty acids serve as ligands for GPR40, and that fatty acids regulate insulin secretion through GPR40. Itoh *et al.* (2003) *Nature* 422:173-176; Briscoe *et al.* (2003) *J. Biol. Chem.* 278: 11303-11311; Kotarsky *et al.* (2003) *Biochem. Biophys. Res. Copmmun.* 301: 406-410.

[0004] The prevalence of type II diabetes, obesity and cardiovascular disease and dyslipidemia underscores the need for new therapies to effectively treat or prevent these conditions.

3. **SUMMARY OF THE INVENTION**

[0005] The invention provides compounds, pharmaceutical compositions and methods useful for treating or preventing conditions and disorders such as type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, cardiovascular disease and atherosclerosis..

[0006] In one aspect, the compounds of the inventions have the general formula (I):



wherein

R¹ is -H, -OH, -NHS(O₂)CH₃, heteroaryl, or -NH-heteroaryl;

R² is -(C₂-C₈)alkyl, -(C₃-C₈)alkenyl, -NR³R⁴, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C≡N, or -C≡C-R⁵;

R³ and R⁴ are independently -H, -(C₁-C₅)alkyl, or -(C₁-C₅)oxyalkyl;

R⁵ is -H, -(C₁-C₅)alkyl, -hetero(C₁-C₅)alkyl, -(C₁-C₅)oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

Z is $\begin{array}{c} \text{H} \\ | \\ -\text{C}- \\ | \\ \text{L} \end{array}$ or $\begin{array}{c} | \\ -\text{N}- \\ | \end{array}$;

L is -O-, -S-, or -N(R⁶)-;

R⁶ is -H, substituted or unsubstituted aryl(C₁-C₁₀)alkyl or substituted or unsubstituted aryl Y is -CH₂- , -CH₂CH₂- , -CH=CH- , -C(O)CH₂- , -C(O)CH₂CH₂- , -C(O)CH=CH- , -S(O₂)CH₂- , -S(O₂)CH₂CH₂- , -S(O₂)CH=CH- , or -C(O)- ; and

W is a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0007] Unless otherwise indicated, the compounds provided in the above formula include pharmaceutically acceptable salts, hydrates or prodrugs thereof.

[0008] In another aspect, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound of formula (I).

[0009] In another aspect, the invention provides methods for treating or preventing a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, cardiovascular disease and atherosclerosis, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

[0010] In another aspect, the invention provides methods for treating or preventing a disease or condition responsive to the modulation of GPR40 comprising administering to a subject in need thereof a therapeutically effective amount of a compound of a compound of any one of formula (I).

[0011] In another aspect, the invention provides methods for treating or preventing a disease or condition mediated, regulated or influenced by pancreatic β cells comprising administering to a subject in need thereof a therapeutically effective amount of a compound of a compound of any one of formula (I).

[0012] In another aspect, the invention provides methods for modulating GPR40 function in a cell, comprising contacting a cell with a compound of formula (I).

[0013] In another aspect, the invention provides methods for modulating GPR40 function comprising contacting GPR40 with a compound of formula (I).

[0014] In another aspect, the invention provides methods for modulating circulating insulin concentration in a subject, comprising administering a compound of formula (I) to the subject.

[0015] Other objects, features and advantages of the invention will become apparent to those skilled in the art from the following description and claims.

4. BRIEF DESCRIPTION OF THE FIGURES

[0016] FIG. 1 provides a scheme for synthesis of exemplary compounds of the invention.

5. DETAILED DESCRIPTION OF THE INVENTION

5.1 Abbreviations and Definitions

[0017] The terms "treat", "treating" and "treatment", as used herein, are meant to include alleviating or abrogating a condition or disease and/or its attendant symptoms and alleviating. The terms "prevent", "preventing" and "prevention", as used herein, refer to a

method of delaying or precluding the onset of a condition or disease and/or its attendant symptoms, barring a subject from acquiring a condition or disease or reducing a subject's risk of acquiring a condition or disease.

[0018] The term "therapeutically effective amount" refers to that amount of the compound that will elicit the biological or medical response of a tissue, system, or subject that is being sought. The term "therapeutically effective amount" includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated in a subject. The therapeutically effective amount in a subject will vary depending on the compound, the disease and its severity and the age, weight, *etc.*, of the subject to be treated.

[0019] The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[0020] The terms "modulate", "modulation" and the like refer to the ability of a compound to increase or decrease the function or activity of GPR40 either directly or indirectly. Inhibitors are compounds that, for example, bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate signal transduction, such as, for instance, antagonists. Activators are compounds that, for example, bind to, stimulate, increase, activate, facilitate, enhance activation, sensitize or up regulate signal transduction, such as agonists for instance. Modulation may occur *in vitro* or *in vivo*.

[0021] As used herein, the term "GPR40-mediated condition or disorder" and the like refer to a condition or disorder characterized by inappropriate, for example, less than or greater than normal, GPR40 activity. A GPR40-mediated condition or disorder may be completely or partially mediated by inappropriate GPR40 activity. However, a GPR40-mediated condition or disorder is one in which modulation of GPR40 results in some effect on the underlying condition or disease (*e.g.*, a GPR40 modulator results in some improvement in patient well-being in at least some patients). Exemplary GPR40-mediated conditions and disorders include metabolic disorders, *e.g.*, diabetes, type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, and related disorders, *e.g.*, cardiovascular disease and atherosclerosis.

[0022] The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination

thereof, which is fully saturated, having the number of carbon atoms designated (e.g., C₁-C₁₀ means one to ten carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl and the like.

[0023] The term "alkenyl", by itself or as part of another substituent, means a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (i.e., C₂-C₈ means two to eight carbons) and one or more double bonds. Examples of alkenyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl) and higher homologs and isomers thereof.

[0024] The term "alkynyl", by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (i.e., C₂-C₈ means two to eight carbons) and one or more triple bonds. Examples of alkynyl groups include ethynyl, 1- and 3-propynyl, 3-butynyl and higher homologs and isomers thereof.

[0025] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from alkyl, as exemplified by -CH₂CH₂CH₂CH₂- . Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0026] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively. Similarly, the term dialkylamino refers to an amino group having two attached alkyl groups that can be the same or different.

[0027] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any position of the heteroalkyl group. Examples include -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -CH₂-

$\text{CH}=\text{N}-\text{OCH}_3$, and $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$. When a prefix such as ($\text{C}_2\text{-C}_8$) is used to refer to a heteroalkyl group, the number of carbons (2 to 8, in this example) is meant to include the heteroatoms as well. For example, a C_2 -heteroalkyl group is meant to include, for example, $-\text{CH}_2\text{OH}$ (one carbon atom and one heteroatom replacing a carbon atom) and $-\text{CH}_2\text{SH}$.

[0028] To further illustrate the definition of a heteroalkyl group, where the heteroatom is oxygen, a heteroalkyl group is an oxyalkyl group. For instance, ($\text{C}_1\text{-C}_5$)oxyalkyl is meant to include, for example $-\text{CH}_2-\text{O}-\text{CH}_3$ (a C_3 -oxyalkyl group with two carbon atoms and one oxygen replacing a carbon atom), $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, and the like.

[0029] The term “heteroalkylene” by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alklenedioxy, alkyleneamino, alklenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

[0030] The terms “cycloalkyl” and “heterocycloalkyl”, by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl”, respectively. Thus, the terms “cycloalkyl” and “heterocycloalkyl” are meant to be included in the terms “alkyl” and “heteroalkyl”, respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0031] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl”, are meant to include alkyl substituted with halogen atoms which can be the same or different, in a number ranging from one to $(2m' + 1)$, where m' is the total number of carbon atoms in the alkyl group. For example, the term “halo($\text{C}_1\text{-C}_4$)alkyl” is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. Thus, the term “haloalkyl” includes monohaloalkyl (alkyl substituted with one halogen atom) and polyhaloalkyl (alkyl substituted with halogen atoms in a number ranging from two to $(2m' + 1)$ halogen atoms). The term “perhaloalkyl” means,

unless otherwise stated, alkyl substituted with $(2m' + 1)$ halogen atoms, where m' is the total number of carbon atoms in the alkyl group. For example, the term "perhalo(C₁-C₄)alkyl", is meant to include trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl, and the like.

[0032] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from the group consisting of N, O and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1H-indazole, carbazole, α -carboline, β -carboline, γ -carboline, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl and 8-quinolyl.

[0033] Preferably, the term "aryl" refers to a phenyl or naphthyl group which is unsubstituted or substituted. Preferably, the term "heteroaryl" refers to a pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, indolyl, isoquinolyl, quinoxalinyl or quinolyl group which is unsubstituted or substituted.

[0034] For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxyethyl, 2-pyridyloxymethyl, 3-(1-naphthoxy)propyl, and the like).

[0035] Each of the above terms (e.g., "alkyl," "heteroalkyl," "aryl" and "heteroaryl") is meant to include both substituted and unsubstituted forms of the indicated

radical, unless otherwise indicated. Preferred substituents for each type of radical are provided below.

[0036] Substituents for the alkyl and heteroalkyl radicals (as well as those groups referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R'', -SR', halogen, -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'-C(O)NR'R'', -NR'-SO₂NR'R'', -NR'CO₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -SO₂R', -SO₂NR'R'', -NR'SO₂R, -CN and -NO₂, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred. R', R'' and R''' each independently refer to hydrogen, unsubstituted (C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with one to three halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C₁-C₄)alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. For example, -NR'R'' is meant to include 1-pyrrolidinyl and 4-morpholinyl.

[0037] Typically, an alkyl or heteroalkyl group will have from zero to three substituents, with those groups having two or fewer substituents being preferred in the present invention. More preferably, an alkyl or heteroalkyl radical will be unsubstituted or monosubstituted. Most preferably, an alkyl or heteroalkyl radical will be unsubstituted. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as trihaloalkyl (e.g., -CF₃ and -CH₂CF₃).

[0038] Preferred substituents for the alkyl and heteroalkyl radicals are selected from: -OR', =O, -NR'R'', -SR', halogen, -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'CO₂R', -NR'-SO₂NR'R'', -S(O)R', -SO₂R', -SO₂NR'R'', -NR'SO₂R, -CN and -NO₂, where R' and R'' are as defined above. Further preferred substituents are selected from: -OR', =O, -NR'R'', halogen, -OC(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'CO₂R', -NR'-SO₂NR'R'', -SO₂R', -SO₂NR'R'', -NR'SO₂R, -CN and -NO₂.

[0039] Similarly, substituents for the aryl and heteroaryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR'C(O)R', -NR'C(O)₂R', -NR'-C(O)NR'R'', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'' and R''' are independently selected from hydrogen, (C₁-C₈)alkyl and heteroalkyl,

unsubstituted aryl and heteroaryl, (unsubstituted aryl)-(C₁-C₄)alkyl, and (unsubstituted aryl)oxy-(C₁-C₄)alkyl.

[0040] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CH₂)_s-X-(CH₂)_t-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂- or -S(O)₂NR'. The substituent R' in -NR'- and -S(O)₂NR' is selected from hydrogen or unsubstituted (C₁-C₆)alkyl. Otherwise, R' is as defined above.

[0041] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), and sulfur (S).

[0042] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge *et al.* (1977) *J. Pharm. Sci.* **66**:1-

19). Certain specific compounds of the invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0043] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the invention.

[0044] In addition to salt forms, the invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the invention. Additionally, prodrugs can be converted to the compounds of the invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the invention which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[0045] Certain compounds of the invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the invention. Certain compounds of the invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the invention and are intended to be within the scope of the invention.

[0046] Certain compounds of the invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, enantiomers, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the invention. These isomers can be resolved or asymmetrically synthesized using conventional methods to render the isomers "optically pure", *i.e.*, substantially free of its other isomers.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxilliary, where the resulting diastereomeric mixture is separated and the auxilliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diasteromers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[0047] The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Radiolabeled compounds are useful as therapeutic or prophylactic agents, research reagents, e.g., GPR40 assay reagents, and diagnostic agents, e.g., *in vivo* imaging agents. All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention.

5.2 Embodiments of the Invention

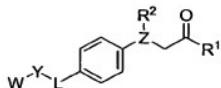
[0048] In one aspect, a class of compounds that modulate GPR40 is described herein. Depending on the biological environment (e.g., cell type, pathological condition of the subject, etc.), these compounds can modulate, e.g., activate or inhibit, the actions of GPR40. By modulating GPR40, the compounds find use as therapeutic agents capable of regulating insulin levels in a subject. The compounds find use as therapeutic agents for modulating diseases and conditions responsive to modulation of GPR40 and/or mediated by GPR40 and/or mediated by pancreatic β cells. As noted above, examples of such diseases and conditions include type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, cardiovascular disease and atherosclerosis. Additionally, the compounds are useful for the treatment and/or prevention of complications of these diseases and disorders (e.g., type II diabetes).

[0049] While the compounds of the invention are believed to exert their effects by interacting with GPR40, the mechanism of action by which the compounds act is not a limiting embodiment of the invention.

[0050] Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein.

5.2.1 Compounds

[0051] In one aspect, the present invention provides a compound having the formula (I):



where R¹, R², Z, L, Y and W are defined below.

[0052] R¹ is -H, -OH, -NHS(O₂)CH₃, heteroaryl, or -NH-heteroaryl. In certain embodiments, R¹ is tetrazolyl, pyrimidinyl, or pyridinyl.

[0053] In preferred embodiments, R¹ is -OH, or a salt thereof.

[0054] R² is -H, -(C₂-C₈)alkyl, -(C₃-C₈)alkenyl, -NR³R⁴, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, —C≡N, or —C≡C-R⁵. In some embodiments, R² is -(C₂-C₈)alkyl, -(C₃-C₈)alkenyl, -NR³R⁴, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, —C≡N, or —C≡C-R⁵.

[0055] In other embodiments, R² is unsubstituted aryl or unsubstituted heteroaryl. In other embodiments, R² is substituted aryl and the substitution onto the aryl is unsubstituted -(C₁-C₅)alkyl, -(C₁-C₅)oxyalkyl, or -halo(C₁-C₅)alkyl.

[0056] In certain embodiments, R² is —C≡C-R⁵ and R⁵ is -(C₁-C₅)alkyl having 0 or 1 heteroatoms. In some embodiments, where a heteroatom is present in the -(C₁-C₅)alkyl group, a proviso is that if W is a benzene ring then the heteroatom is not Si.

[0057] In preferred embodiments, R² is -C≡CCH₃.

[0058] In some embodiments, R² is -CH=C(CH₃)₂, or -CH₂CH=CH₂.

[0059] R³ and R⁴ are independently -H, -(C₁-C₅)alkyl, or -(C₁-C₅)oxyalkyl.

[0060] R⁵ is -H, -(C₁-C₅)alkyl, -hetero(C₁-C₅)alkyl, -(C₁-C₅)oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0061] In some embodiments, R⁵ is -(C₁-C₅)alkyl, -(C₁-C₅)oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R⁵ is -(C₁-C₅)alkyl that does not contain Si.

[0062] In some embodiments, R⁵ is unsubstituted phenyl.

[0063] In other embodiments, R⁵ is a substituted phenyl.

[0064] In preferred embodiments, R⁵ is methyl.

[0065] In some embodiments, where R¹ is -OH, L is -O-, Y is -CH₂-, and W is *para*-methoxyphenyl, then R⁵ is not -H.

[0066] Z is $\begin{array}{c} \text{H} \\ | \\ -\text{C}- \end{array}$ or $-\text{N}-$. In some embodiments, Z is nitrogen. In other embodiments, Z is carbon.

[0067] L is -O-, -S-, or -N(R⁶)-. In some embodiments, L is -O-. In other embodiments, L is -S-. In other embodiments, L is -N(R⁶)-.

[0068] R⁶ is -H, substituted or unsubstituted aryl(C₁-C₁₀)alkyl or substituted or unsubstituted aryl.

[0069] In some embodiments, R⁶ is -H.

[0070] In other embodiments, R⁶ is substituted or unsubstituted phenyl.

[0071] Y is -CH₂- , -CH₂CH₂- , -CH=CH- , -C(O)CH₂- , -C(O)CH₂CH₂- , -C(O)CH=CH- , -S(O)₂CH₂- , -S(O)₂CH₂CH₂- , -S(O)₂CH=CH- , or -C(O)-.

[0072] In some embodiments Y is -CH₂-.

[0073] In some embodiments where L is -O- or -S-, Y is -CH₂- , -CH₂CH₂-.

[0074] In certain embodiments, a proviso exists that where L is -N(R⁶)-, Z is nitrogen, R² is a phenyl, and W is a phenyl, then Y is not -C(O)-.

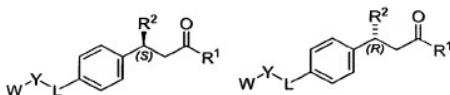
[0075] W is a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0076] In some embodiments, W is substituted or unsubstituted fused aryl bicyclic ring or substituted or unsubstituted fused heteroaryl bicyclic ring.

[0077] In other embodiments, W is a substituted or unsubstituted 5- or 6-membered aryl ring or substituted or unsubstituted 5- or 6-membered heteroaryl ring.

[0078] Unless otherwise indicated, the compounds provided in the above formula include pharmaceutically acceptable salts, hydrates or prodrugs thereof.

[0079] In some embodiments, Z is carbon and R² is -(C₂-C₈)alkyl, -(C₃-C₈)alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or $-\text{C}\equiv\text{C}-\text{R}^5$. It will be apparent that the carbon at Z is a chiral carbon as shown:

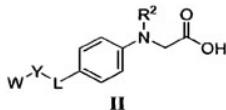


Thus, a compound of the invention may be a S-enantiomer, a R-enantiomer, or a mixture of both a S-enantiomer and a R-enantiomer.

[0080] In preferred embodiments, a compound is a S-enantiomer.

[0081] In other embodiments, L is -O-, -S-, and Y is -CH₂- , or -CH₂CH₂-.

[0082] In certain embodiments, the present invention provides a compound having the formula (II):



or a pharmaceutically acceptable salt, hydrate or prodrug thereof, where R², L, Y, and W are defined as above.

[0083] In some embodiments R² is -H, -(C₂-C₃)alkyl, -NR³R⁴, or substituted or unsubstituted phenyl.

[0084] L is -O-, -S-, or -N(R⁶)-.

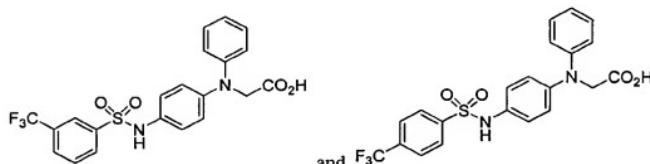
[0085] R⁶ is -H, substituted or unsubstituted aryl(C₁-C₁₀)alkyl or substituted or unsubstituted aryl.

[0086] Y is -CH₂- , -CH₂CH₂- , -CH=CH- , -C(O)CH₂- , -C(O)CH₂CH₂- , -C(O)CH=CH- , -S(O)₂CH₂- , -S(O)₂CH₂CH₂- , -C(O)-, or -S(O)₂CH=CH- .

[0087] W is a substituted or unsubstituted 5- or 6-membered aryl ring or substituted or unsubstituted 5- or 6-membered heteroaryl ring with the proviso if R² is phenyl and W is a benzene ring then Y may not be -C(O)-.

[0088] In some embodiments, L is -N(R⁶)-; and R⁶ is hydrogen.

[0089] In other embodiments, the compound of formula (II) is selected from the group consisting of



or a salt thereof.

[0090] In further embodiments, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein R¹ is -OH, -NHS(O₂)CH₃, -NH-tetrazole, or tetrazole; R² is -(C₂-C₃)alkyl, -NR³R⁴, substituted or unsubstituted phenyl, -CH=C(CH₃)₂, -CH₂CH=CH₂, or -C≡C-R⁵; R³ and R⁴ are independently -H, -(C₁-C₅)alkyl, or -(C₁-C₅)oxyalkyl; R⁵ is -(C₁-C₅)alkyl, -(C₁-C₅)oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; Z is

$\begin{array}{c} \text{H} \\ | \\ -\text{C}- \end{array}$ or $\begin{array}{c} | \\ -\text{N}- \end{array}$; L is -O-, -S-, or -N(R⁶)-; R⁶ is -H, substituted or unsubstituted aryl(C₁-C₁₀)alkyl or substituted or unsubstituted aryl; Y is -CH₂- , -CH₂CH₂- , -CH=CH- , -C(O)CH₂- , -C(O)CH=CH- , -S(O)₂CH₂- , -S(O)₂CH₂CH₂- , or

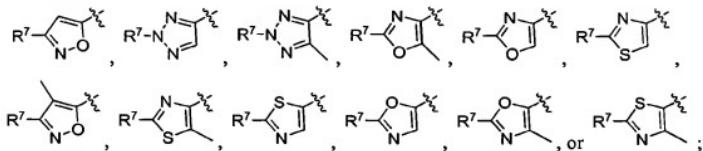
-S(O)₂CH=CH-; and W is a substituted or unsubstituted 5- or 6-membered aryl ring or substituted or unsubstituted 5- or 6-membered heteroaryl ring.

- [0091] In some embodiments, R¹ is -OH; L is -O-, or -S-; and Y is -CH₂- , or -CH₂CH₂- .

[0092] In other embodiments, W is a substituted or unsubstituted phenyl.

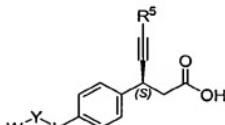
[0093] In other embodiments, W is substituted with substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted hetero(C₁-C₁₀)alkyl, substituted or unsubstituted halo(C₁-C₁₀)alkyl, substituted or unsubstituted aryl(C₁-C₁₀)alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0094] In other embodiments, W is a 5-membered ring selected from the group consisting of



and R⁷ is substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted hetero(C₁-C₁₀)alkyl, substituted or unsubstituted halo(C₁-C₁₀)alkyl, substituted or unsubstituted aryl(C₁-C₁₀)alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

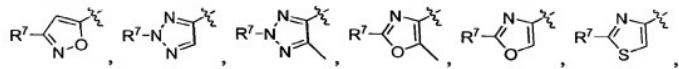
- [0095] In certain embodiments, the present invention provides compounds according to formula (III):

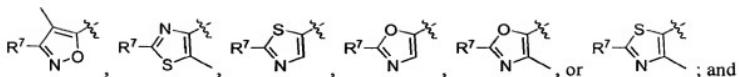


III

or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein R⁵, W, Y, and L are defined as above.

- [0096] In some embodiments, R⁵ is methyl.
[0097] In other embodiments, L is -O- or -S- and Y is -CH₂- or -CH₂CH₂-.
[0098] In other embodiments, W is a 5-membered ring selected from the group consisting of



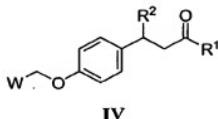


R^7 is substituted or unsubstituted (C_1 - C_{10})alkyl, substituted or unsubstituted hetero(C_1 - C_{10})alkyl, substituted or unsubstituted halo(C_1 - C_{10})alkyl, substituted or unsubstituted aryl(C_1 - C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0099] In other embodiments, R^7 is substituted phenyl.

[00100] In other embodiments, R^7 is unsubstituted phenyl.

[00101] In certain embodiments, the present invention provides compounds according to formula (IV):



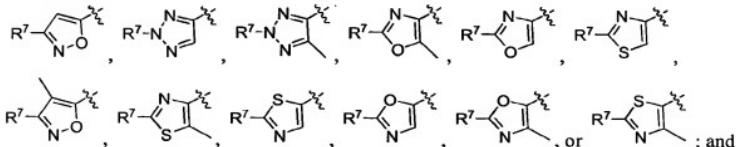
or a pharmaceutically acceptable salt, hydrate or prodrug thereof, where R^1 , R^2 and W are defined as above, paragraph [0090].

[00102] In some embodiments, R^1 is -OH, or a salt thereof.

[00103] In other embodiments, W is substituted phenyl.

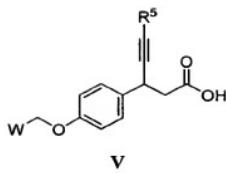
[00104] In other embodiments, W is substituted with substituted or unsubstituted (C_1 - C_{10})alkyl, substituted or unsubstituted hetero(C_1 - C_{10})alkyl, substituted or unsubstituted halo(C_1 - C_{10})alkyl, substituted or unsubstituted aryl(C_1 - C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00105] In other embodiments, W is a 5-membered ring selected from the group consisting of



R^7 is substituted or unsubstituted (C_1 - C_{10})alkyl, substituted or unsubstituted hetero(C_1 - C_{10})alkyl, substituted or unsubstituted halo(C_1 - C_{10})alkyl, substituted or unsubstituted aryl(C_1 - C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

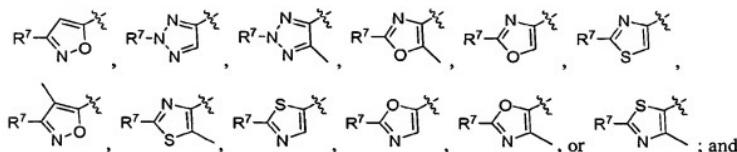
[00106] In certain embodiments, the present invention provides compounds according to formula (V):



or a pharmaceutically acceptable salt, hydrate or prodrug thereof, where R⁵ and W are defined in paragraph [0090] above.

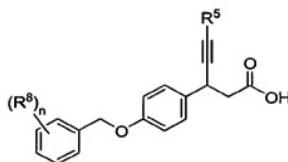
[00107] In some embodiments, R⁵ is methyl.

[00108] In other embodiments, W is a 5-membered ring selected from the group consisting of



R⁷ is hydrogen, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted hetero(C₁-C₁₀)alkyl, substituted or unsubstituted halo(C₁-C₁₀)alkyl, substituted or unsubstituted aryl(C₁-C₁₀)alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00109] In certain embodiments, the present invention provides compounds according to formula (VI):



or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein each R⁸ is independently selected from the group consisting of substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted hetero(C₁-C₁₀)alkyl, substituted or unsubstituted halo(C₁-C₁₀)alkyl, substituted or unsubstituted aryl(C₁-C₁₀)alkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, the subscript n is an integer from 0 to 5, and R⁵ is as defined above.

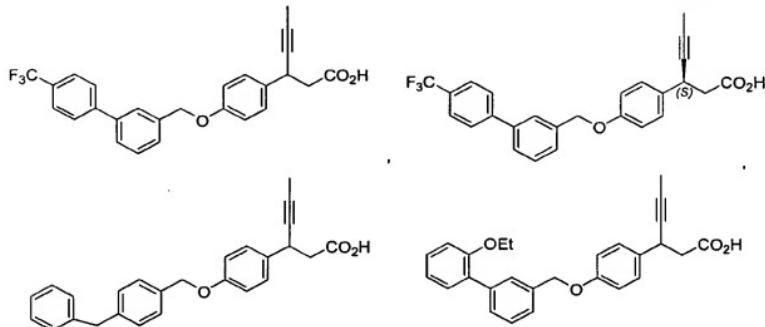
[00110] In some embodiments, the subscript n is 0, 1, or 2.

[00111] In other embodiments, R⁸ is a methoxy, ethoxy, trihalomethyl, methyl, halo, or cyano group and the subscript n is 1 or 2.

[00112] In other embodiments, R⁸ is a phenyl, methoxyphenyl, methylphenyl, trihalomethylphenyl, benzyl, phenoxy, ethoxyphenyl, cyanophenyl, halophenyl, halobenzyl, pyridyl, methoxybenyl, or pyrlyl group and the subscript n is 1 or 2.

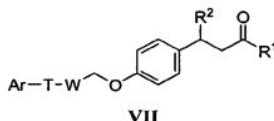
[00113] In other embodiments, R⁵ is methyl.

[00114] In other embodiments, the formula is selected from the group consisting of



and salts thereof.

[00115] In certain embodiments, the present invention provides compounds according to formula (VII):



VII

or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein R¹, R² and W are defined in paragraph [0090] above, T is a direct bond, substituted or unsubstituted (C₁-C₅)alkyl or substituted or unsubstituted hetero(C₁-C₅)alkyl, and Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

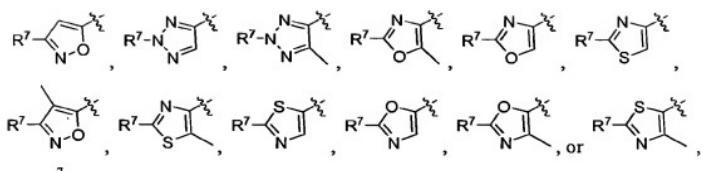
[00116] In some embodiments, R² is -C≡C-CH₃.

[00117] In other embodiments, R¹ is -OH.

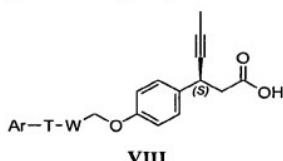
[00118] In other embodiments, T is a direct bond and Ar is a substituted or unsubstituted benzene ring.

[00119] In other embodiments, W is phenyl.

[00120] In other embodiments, W is a 5-membered ring selected from the group consisting of

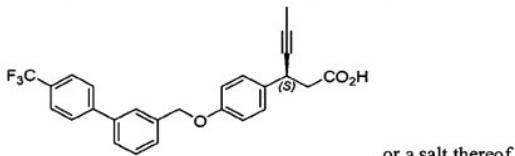


[00121] In other embodiments, certain embodiments, the present invention provides compounds according to formula (VIII)

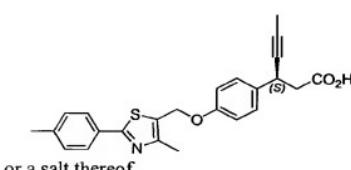
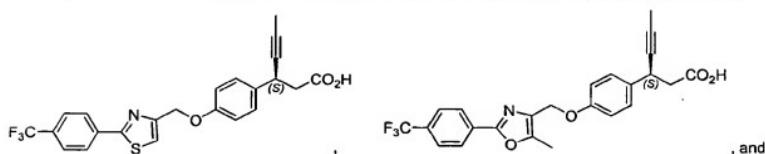


or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein W, T and Ar are as defined above.

[00122] In some embodiments, the compound has the formula:



[00123] In an embodiment, the compound is selected from the group consisting of:



5.2.2 Preparation of the Compounds

[00124] Exemplary synthesis routes to the compounds provided herein are described in the Examples. One of skill in the art will understand that the synthetic routes can be modified to use different starting materials and/or alternate reagents to accomplish the desired transformations. Additionally, one of skill in the art will recognize that protecting groups may be necessary for the preparation of certain compounds and will be aware of those conditions compatible with a selected protecting group. Accordingly, the methods and reagents described herein are all expressed as non-limiting embodiments.

5.2.3 Compositions

[00125] In another aspect, the invention provides pharmaceutical compositions suitable for pharmaceutical use comprising one or more compounds of the invention and a pharmaceutically acceptable carrier, excipient or diluent.

[00126] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients (and in the specified amounts, if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant that the carrier or excipient is compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[00127] In certain embodiments, the present inventions provides a pharmaceutical compositions comprising a compound of formula (I), wherein R² comprises an alkylyl containing Si, and where R¹, L, Y, and W are as defined above.

[00128] In some embodiments, the Si atom is substituted with up to three alkyl groups.

[00129] In some embodiments, R² is -C≡C-Si(CH₃)₃.

[00130] Composition formulation may improve one or more pharmacokinetic properties (e.g., oral bioavailability, membrane permeability) of a compound of the invention (herein referred to as the active ingredient).

[00131] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired

formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

[00132] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,256,108; 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for control release.

[00133] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[00134] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as

polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[00135] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[00136] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[00137] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[00138] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[00139] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents

that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00140] The pharmaceutical compositions may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[00141] For topical use, creams, ointments, jellies, solutions or suspensions, *etc.*, containing the compounds of the invention are employed. As used herein, topical application is also meant to include the use of mouthwashes and gargles.

[00142] The pharmaceutical compositions and methods of the invention may further comprise other therapeutically active compounds, as noted herein, useful in the treatment of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, cardiovascular disease and atherosclerosis.

5.2.4 Methods of Use

[00143] In another aspect, the invention provides methods of treating or preventing a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, cardiovascular disease and atherosclerosis, comprising administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention.

[00144] In one embodiment, the disease or condition is type II diabetes.

[00145] In another aspect, the present invention provides a method for treating a disease or condition responsive to the modulation of GPR40 comprising administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention.

[00146] In some embodiments, the disease or condition is selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin

resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, cardiovascular disease and atherosclerosis.

[00147] In preferred embodiments, the disease or condition is type II diabetes.

[00148] In some embodiments, the disease or condition is obesity.

[00149] In some embodiments of administering the compounds or compositions or the invention, the compound or composition is administered orally.

[00150] In other embodiments, the compound or composition is administered parentally.

[00151] In other embodiments, the compound or composition is administered in combination with a second therapeutic agent.

[00152] In preferred embodiments, the second therapeutic agent is a metformin or a thiazolidinedione.

[00153] In another aspect, the invention provides methods of treating or preventing a disease or disorder responsive to modulation of GPR40 comprising administering to a subject having such a disease or disorder, a therapeutically effective amount of one or more of the subject compounds or compositions.

[00154] In yet another aspect, the invention provides methods of treating or preventing a disease or disorder mediated GPR40 comprising administering to a subject having such a condition or disease, a therapeutically effective amount of one or more of the subject compounds or compositions.

[00155] In yet another aspect, the invention provides methods of modulating GPR40 comprising contacting a cell with one or more of the subject compounds or compositions.

[00156] Depending on the disease to be treated and the subject's condition, the compounds of the invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal, local) routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. The invention also contemplates administration of the compounds of the invention in a depot formulation, in which the active ingredient is released over a defined time period.

[00157] In the treatment or prevention type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and

dyslipidemia, cardiovascular disease and atherosclerosis or other conditions or disorders associated with GPR40, an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

[00158] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[00159] The compounds of the invention can be combined or used in combination with other agents useful in the treatment, prevention, suppression or amelioration of the diseases or conditions for which compounds of the invention are useful, including type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, cardiovascular disease and atherosclerosis. Such other agents, or drugs, may be administered, by a route and in an amount commonly used therefor, simultaneously or sequentially with a compound of the invention. When a compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the invention is preferred. Accordingly, the pharmaceutical compositions of the invention include those that also contain one or more other active ingredients or therapeutic agents, in addition to a compound of the invention.

[00160] Examples of other therapeutic agents that may be combined with a compound of the invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) cholesterol lowering agents such as HMG-

CoA reductase inhibitors (*e.g.*, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and other statins), bile acid sequestrants (*e.g.*, cholestyramine and colestipol), vitamin B₃ (also known as nicotinic acid, or niacin), vitamin B₆ (pyridoxine), vitamin B₁₂ (cyanocobalamin), fibrin acid derivatives (*e.g.*, gemfibrozil, clofibrate, fenofibrate and benzafibrate), probucol, nitroglycerin, and inhibitors of cholesterol absorption (*e.g.*, betasitosterol and acylCoA-cholesterol acyltransferase (ACAT) inhibitors such as melinamide), HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and squalene synthetase inhibitors; (b) antithrombotic agents, such as thrombolytic agents (*e.g.*, streptokinase, alteplase, anistreplase and reteplase), heparin, hirudin and warfarin derivatives, β -blockers (*e.g.*, atenolol), β -adrenergic agonists (*e.g.*, isoproterenol), ACE inhibitors and vasodilators (*e.g.*, sodium nitroprusside, nicardipine hydrochloride, nitroglycerin and enaloprilat); and (c) anti-diabetic agents such as insulin and insulin mimetics, sulfonylureas (*e.g.*, glyburide, meglitinide), biguanides, *e.g.*, metformin (*Glucophage*[®]), α -glucosidase inhibitors (acarbose), thiazolidinone compounds, *e.g.*, rosiglitazone (*Avandia*[®]), troglitazone (*Rezulin*[®]), ciglitazone, pioglitazone (*Actos*[®]) and englitazone.

[00161] The weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Combinations of a compound of the invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[00162] In another aspect, the present invention provides a method for modulating circulating insulin concentration in a subject, comprising administering a compound or composition of the invention.

[00163] In some embodiments, the insulin concentration is increased.

[00164] In other embodiments, the insulin concentration is decreased.

[00165] In certain embodiments, a compound, or composition comprising a compound, according to formula (I) wherein R² comprises an alkyl containing Si, and where R¹, L, Y, and W are as defined above, may be used.

[00166] In some embodiments, the Si atom is substituted with up to three alkyl groups.

[00167] In some embodiments, R² is -C≡Si(CH₃)₃.

[00168] The following examples are offered by way of illustration and are not intended to limit the scope of the invention. Those of skill in the art will readily recognize a variety of noncritical parameters that could be modified to yield essentially similar results.

6. EXAMPLES

6.1 Example 1

[00169] This example illustrates the preparation of (*3S*)-3-(4-Hydroxy-phenyl)-hex-4-ynoic acid methyl ester.

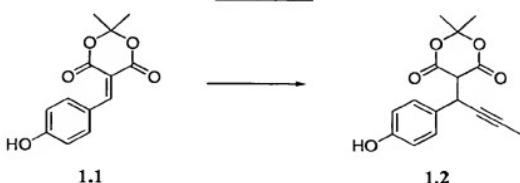
Scheme 1.1



[00170] **5-(4-Hydroxy-benzylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.1).**

Condensation with Meldrum's acid is carried out according to the method of Bigi *et. al.* (Tetr. Lett. 2001, 42, 5203-5205). A 2L pear-shaped flask was charged with 4-hydroxybenzaldehyde (50 g, 409 mmol) and water (400 mL). The flask was placed in a water bath at 75 °C and Meldrum's acid (62 g, 430 mmol) was added as a slurry in 400 mL of water. The reaction mixture was agitated for 2 h then cooled in an ice bath for 2 hours. The product was collected by filtration and rinsed with cold water. After drying thoroughly, 95 g (94%) of adduct 1.1 was obtained as a fine yellow powder.¹H NMR(500MHz)(DMSO-d₆) δ 9.75 (br s, 1H); 8.27 (s, 1H); 8.24 (d, 2H, J=10 Hz); 6.98 (d, 2H, J=10 Hz); 1.76 (s, 6H). MS ESI (pos.) m/e: 519.0 (2M + Na).

Scheme 1.2



[00171] **(+/-)-5-[1-(4-Hydroxy-phenyl)-but-2-ynyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (1.2).** An oven-dried 3L 3-neck flask equipped with a mechanical stirrer, nitrogen inlet, nitrogen outlet and placed in a room-temperature water bath. After purging with nitrogen for 20 minutes, a solution of 1-propynylmagnesium bromide in THF (0.5 N, 600 mL) was added by cannula. In a separate oven-dried and nitrogen-flushed 500 mL RB

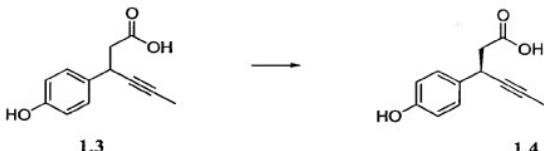
flask, compound 1.1 (35 g, 142 mmol) was dissolved in anhydrous THF (350 mL) with gentle warming. The solution of 1.1 was then added over 15 minutes. Over the course of the addition, the reaction mixture changed to a thick, yellow suspension. After the addition was complete, the reaction mixture was stirred for 15 minutes and then quenched with aqueous NH₄Cl (0.6N, 750 mL) and diluted with hexanes (800 mL). The layers were separated and the organic layer discarded. The aqueous layer was acidified to pH ~2 with saturated aqueous KHSO₄ and extracted with ethyl acetate (2 x 400 mL). The combined extracts were washed with saturated brine, dried over MgSO₄, filtered, and concentrated to a light yellow solid (37 g, 91%). ¹H NMR(500MHz)(acetone-*d*₆) δ 8.26 (s, 1H); 7.39 (d, 2H, *J*=8.5 Hz); 6.76 (d, 2H, *J*=8.4 Hz); 4.73 (br s, 1H); 4.46 (d, 1H, *J*=2.4 Hz); 1.82 (s, 3H); 1.81 (s, 3H); 1.64 (s, 3H). MS ESI (pos.) m/e: 599.0 (2M + Na).

Scheme 1.3



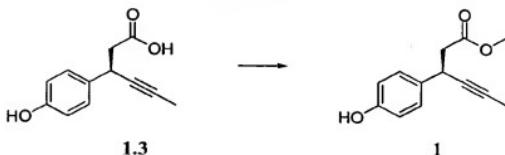
[00172] (+/-)-3-(4-Hydroxy-phenyl)-hex-4-yneoic acid (1.3) A 1L RB flask was charged with compound 1.2 (37 g), diethyl ketone (160 mL), and water (80 mL). The suspension was heated to reflux for 48h. After cooling, the aqueous layer was saturated with NaCl_(s) and separated. The organic layer was dried over MgSO₄, filtered, and concentrated to a light brown oil which was crystallized from hot ethyl acetate:hexanes (1:2). After collecting and drying, the product was obtained as an off-white powder (20.3 g, 77%). ¹H NMR(500MHz)(DMSO-*d*₆) δ 12.2 (s, 1H); 9.27 (s, 1H); 7.12 (d, 2H, *J*=8.5 Hz); 6.67 (d, 2H, *J*=8.6 Hz); 3.87 (m, 1H); 2.54 (m, 2H); 1.82 (d, 3H, *J*=2.4 Hz). MS ESI (pos.) m/e: 205.1 (M + H); 227.1 (M + Na).

Scheme 1.4



[00173] **(3S)-3-(4-Hydroxy-phenyl)-hex-4-ynoic acid (1.4)** A 5L RB flask was charged with compound **1.3** (66.4 g, 325 mmol) and 2-propanol (1 L) and then heated to 70 °C. *(1S, 2R)-1-amino-2-indanol* (46.1 g, 309 mmol) was dissolved in 2-propanol (1 L) with gentle warming. The solution of amine was added to the dissolved carboxylic acid and the resulting solution was allowed to cool to room temperature. After 16h, the crystals were collected and dried. The salt was re-suspended in 2 L of 2-propanol and dissolved by heating to reflux. After allowing to cool to room temperature, the salt was collected after 16h. A small sample of the salt was decomposed with aqueous acid and the free carboxylic acid was analyzed by chiral HPLC (Daicel ChiralPAK AD-H column, eluant: 0.1% TFA in 90:10 hexanes:2-propanol) and was found to have 75% ee. The salt was re-suspended in 1.5 L of 2-propanol and dissolved by heating to reflux. After allowing to cool to room temperature, the salt was collected after 16h. This material was found to have 96% ee by chiral HPLC. This material was suspended in ethyl acetate (300 mL) and water (100 mL). Saturated aqueous KHSO₄ (100 mL) was added with vigorous mixing. After two clear layers were obtained, the layers were separated and the aqueous layer extracted with ethyl acetate (100 mL). The combined extracts were washed with saturated brine, dried over MgSO₄, filtered, and concentrated to a light yellow oil which crystallized on drying *in vacuo*. Compound **1.4** was obtained as an off-white solid (23.5 g, 35%).

Scheme 1.5



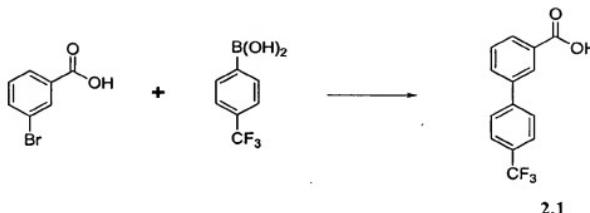
[00174] **(3S)-3-(4-Hydroxy-phenyl)-hex-4-ynoic acid methyl ester (1).** Phenol **1.4** (23.5 g, 115 mmol) was dissolved in acetone (230 mL) and treated with KHCO₃ (11.5 g, 115 mmol). After 15 minutes, methyl iodide (5 mL, 80 mmol) was added, and the reaction stirred at 40 °C for 14h. An additional portion of methyl iodide (3 mL, 48 mmol) was added and heating was continued for 24h. Potassium salts were removed by filtration and thoroughly rinsed with acetone. The filtrate was concentrated to an oil which was purified by filtration through a 1 cm plug of silica gel. Elution with 2.5% MeOH in dichloromethane followed by concentration provided phenol **1** (21.5 g, 85%) as a light

yellow oil. ^1H NMR(500MHz)(acetone- d_6) δ 8.2 (br s, 1H); 7.20 (d, 2H, $J=9.5$ Hz); 6.77 (d, 2H, $J=9.0$ Hz); 3.98 (m, 1H); 3.60 (s, 3H); 2.65 (m, 2H); 1.78 (d, 3H, $J=2.5$ Hz). MS ESI (pos.) m/e: 219.1 ($M + H$); 241.1 ($M + Na$).

6.2 Example 2

[00175] This example illustrates the preparation of (3*S*)-3-[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-hex-4-yanoic acid sodium salt.

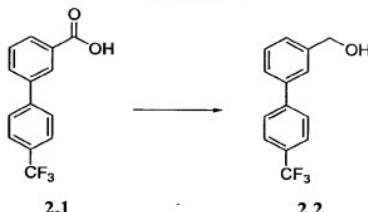
Scheme 2.1



2.1

[00176] **3-(4-Trifluoromethylphenyl)-benzoic acid (2.1).** The Suzuki coupling was carried out according to the method of Dyer et al. (*Tetrahedron Letters*, 2001, **42**, 1765-1767). Commercially available 4-(Trifluoromethyl)phenylboronic acid (15g, 78.7 mmol) and 3-bromobenzoic acid (15.1g, 75 mmol) were suspended in 2-propanol:water (1:4, 72 mL). 10% Pd/C (1.5g) was added followed by aqueous Na_2CO_3 (39 mL, 20% by wt.). The resulting mixture was heated at 70°C for 4 hours. The precipitate was filtered and rinsed with 20% aqueous Na_2CO_3 solution. The filtrate was diluted with water and acidified to pH=2. The white solid was filtered and dried *in vacuo*. The crude material (2.1) (19.69g) was used in the next step without further purification.

Scheme 2.2

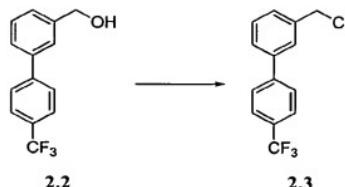


2.1

2.2

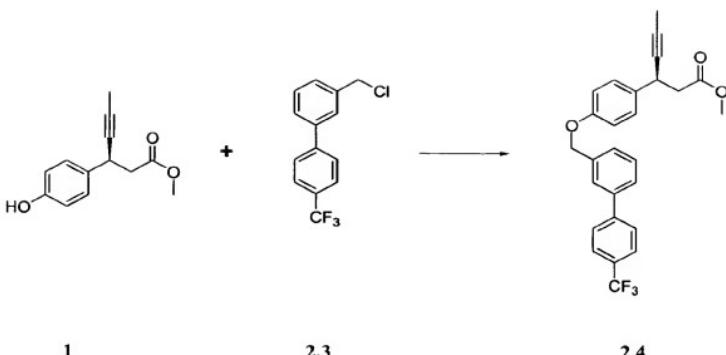
[00177] **3-(4-Trifluoromethylphenyl)-benzyl alcohol (2.2).** The carboxylic acid **2.1** (13.3g, 50mmol) in anhydrous THF (100mL) was added dropwise to LiAlH₄ (2.9g, 75mmol) in anhydrous THF (150mL) at 0°C over 30 minutes. The resulting mixture was slowly warmed to room temperature and stirred for 4 hours. The reaction was slowly quenched with water (2.9mL) at 0°C, 15% NaOH aqueous solution (2.9mL) and another portion of water (8.7mL). The mixture was dried over Na₂SO₄ and concentrated to give a white solid (11.9g). The crude product (**2.2**) was used in the next step without further purification.

Scheme 2.3



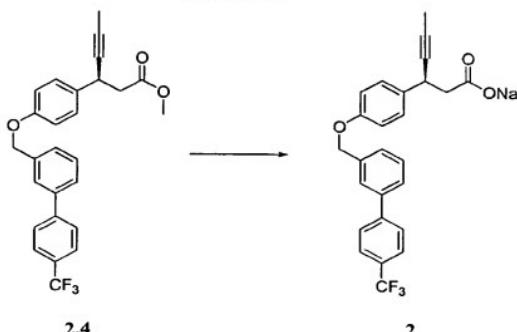
[00178] **3-(4-Trifluoromethylphenyl)-benzyl chloride (2.3).** The alcohol **2.2** (15g, 59.5mmol) was dissolved in anhydrous dichloromethane (100mL). Thionyl chloride (10mL) was slowly added dropwise to the above solution. The resulting mixture was stirred at room temperature for 24 hours. The organic solvent was removed under *vacuo*. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 20% DCM in hexanes). Fractions containing the desired product **2.3** were combined and concentrated to a white solid (14.0 g). ¹H NMR (400MHz) (CDCl₃) δ 7.73 (4H, s); 7.65 (1H, s); 7.58 (1H, s); 7.52-7.28 (2H, m); 4.69 (2H, s).

Scheme 2.4



[00179] **(3*S*)-3-[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-hex-4-ynoic acid methyl ester (2.4).** Benzyl chloride 2.3 (28.0 g, 103 mmol) and phenol 1 (21.5 g, 98 mmol) were dissolved in acetone (150 mL) and treated with Cs₂CO₃ (39.9 g, 122 mmol). The reaction was stirred at 50 °C for 16 h then filtered and concentrated to an pale yellow oil which was purified by column chromatography (silica gel, 33% to 66% dichloromethane in hexanes). Eluant containing compound 2.4 was concentrated to a colorless oil (40.0 g, 92%).

Scheme 2.4

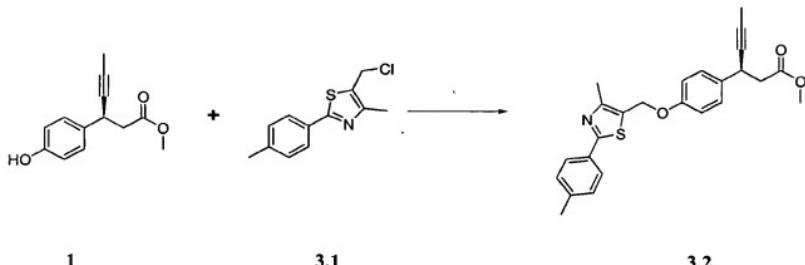


[00180] **(3*S*)-3-[4-(4'-Trifluoromethyl-biphenyl-3-ylmethoxy)-phenyl]-hex-4-ynoic acid sodium salt (2).** Methyl ester 2.4 was dissolved in diethyl ether (50 mL). Sodium trimethylsilanolate (0.78 g, 7 mmol) was added in one portion and the reaction

mixture stirred for 48h. The precipitate was collected by filtration and recrystallized from ethyl acetate:hexanes. After drying *in vacuo*, the desired sodium salt was obtained as a white powder (1.3 g). ¹H NMR (500MHz) (CD₃OD) δ 7.82 (d, 2H, *J*=8.5 Hz); 7.75-7.73 (m, 3H); 7.62 (m, 1H); 7.32 (d, 2H, *J*=8.5 Hz); 6.94 (d, 2H, *J*=8.5 Hz); 5.15 (s, 2H); 4.03 (m, 1H); 2.52 (dd, 1H, *J*=8.2, 14.5 Hz); 2.45 (dd, 1H, *J*=7.0, 14.0 Hz); 1.79 (d, 3H, *J*=2.5 Hz).

6.3 Example 3

Scheme 3.1



[00181] **(3*S*)-3-[4-(4-Methyl-2-p-tolyl-thiazol-5-ylmethoxy)-phenyl]-hex-4-yneoic acid methyl ester (3.2).** Compound 3.1 was prepared according to the method described in example 2 starting from the commercial available 4-methyl-2-(4-methylphenyl)-1,3-thiazole-5-carboxylic acid. The chloride 3.1 (250mg, 1.1 mmol) and phenol 1 (230mg, 1.1mmol) were dissolved in anhydrous DMF (5 mL). Finely powdered Cs₂CO₃ (650mg 2.2mmol) was then added and the reaction mixture was stirred at room temperature for 14 h. The reaction was poured into water and extracted with ethyl acetate (15mL × 3). The organic phases were combined, dried over Na₂SO₄, and concentrated *in vacuo* to a residue which was used in the next step without further purification.

Scheme 3.1



3.2

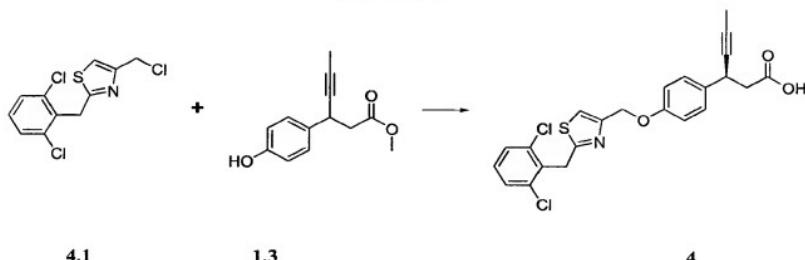
3

[00182] (*S*)-3-[4-(4-Methyl-2-p-tolyl-thiazol-5-ylmethoxy)-phenyl]-hex-4-ynoic acid (3). Ester 3.2 was dissolved in THF/MeOH/10% NaOH_(aq) (1:1:1) solution (15mL). After stirring at room temperature over 30 minutes, the mixture was acidified with 1N HCl (aq.) until pH = 4. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over Na₂SO₄ and concentrated. The crude residue was triturated with 20% ethyl acetate in hexanes (20 mL). The precipitate was filtered and compound 3 was acquired as a pale yellow powder (315mg, 0.8mmol). MS ESI m/e: 406 (M-H). ¹H NMR (500MHz) (CDCl₃) δ 7.86 (2H, d, *J*=7.5 Hz); 7.36 (2H, d, *J*=9 Hz); 7.26 (2H, d, *J*=8 Hz); 6.96 (2H, d, *J*=8.5 Hz); 5.18 (2H, s); 4.1 (1H, m); 2.77 (2H, m); 2.52 (3H, s); 2.42 (3H, s); 1.86 (3H, s).

6.4 Example 4

[00183] This example illustrates the preparation of 3-[4-[2-(2,6-Dichloro-benzyl)-thiazol-4-ylmethoxy]-phenyl]-hex-4-ynoic acid.

Scheme 4.1



4.1

1.3

4

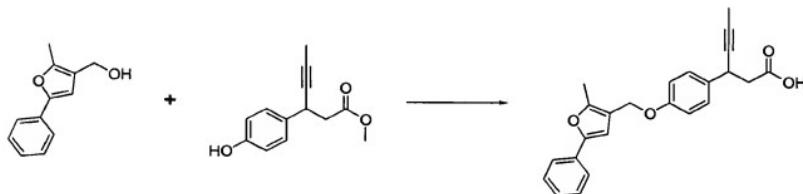
[00184] 3-[4-[2-(2,6-Dichloro-benzyl)-thiazol-4-ylmethoxy]-phenyl]-hex-4-yne-3-carboxylic acid (4). Preparation of thiazole 4.1 was carried out according to the method of Bordwell *et*

al. (*J. Amer. Chem. Soc.*, 1990, **112**, 792-797.). Compound **4.1** (58mg, 0.2mmol) and phenol **1** (43.6mg, 0.2mmol) were dissolved in anhydrous DMF (2mL) and treated with finely powdered Cs₂CO₃ (65mg 0.22mmol). The reaction mixture was stirred at room temperature for 14 hours. The reaction was poured into water and extracted with ethyl acetate (10mL × 3). The combined organic phases were dried over Na₂SO₄, concentrated *in vacuo* and the residue dissolved in THF/MeOH/10% NaOH_(aq) (1:1:1) solution (6 mL). The resulting mixture was stirred at room temperature for 30 minutes. The mixture was acidified with 1N HCl_(aq) until pH = 4. The aqueous phase was extracted with ethyl acetate. The organic phases were combined, dried over Na₂SO₄, and concentrated *in vacuo*. The crude residue was triturated with 20% ethyl acetate in hexanes (10 mL). The precipitate was filtered and acid **4** was acquired as a pale yellow powder (55mg, 0.12mmol). MS ESI m/e: 460 (M-H). ¹H NMR (400MHz) (CDCl₃) δ 7.40-7.19 (6H, m); 6.94-6.79 (2H, m); 5.18 (2H, s); 4.73 (2H, s); 4.1-4.06 (1H, m); 2.77 (2H, m); 1.85 (3H, s).

6.5 Example 5

[00185] This example illustrates the preparation of 3-[4-(2-Methyl-5-phenyl-furan-3-ylmethoxy)-phenyl]-hex-4-ynoic acid.

Scheme 5.1



5.1

1.3

5

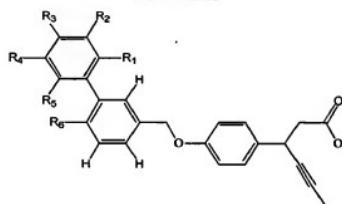
[00186] **3-[4-(2-Methyl-5-phenyl-furan-3-ylmethoxy)-phenyl]-hex-4-ynoic acid (5).** The Mitsunobu reaction was carried out according to the method of Mikó et al. (*J. Med. Chem.* 2003, **46**, 1523-1530). Commercially available **5.1** (37.6mg, 0.2mmol), PPh₃ (52mg, 0.2mmol) and phenol **1.3** (43.6mg, 0.2mmol) were added to anhydrous THF (3mL). DEAD (45μL, 0.22mmol) was then added dropwise. The reaction mixture was stirred at room temperature over 14 hours. The reaction was then extracted with ethyl acetate (10mL × 3). The organic phases were combined, dried over Na₂SO₄, and concentrated *in vacuo*. The resulting residue was dissolved in THF/MeOH/10% NaOH_(aq) (1:1:1) solution (6 mL).

The resulting mixture was stirred at room temperature over 30 minutes. The resulting mixture was stirred at room temperature for 30 minutes. The mixture was acidified with 1N HCl_(aq) until pH = 4. The aqueous phase was extracted with ethyl acetate. The organic phases were combined, dried over Na₂SO₄, and concentrated *in vacuo*. The crude product was triturated in 20% ethyl acetate in hexanes (10 mL). The precipitate was filtered and compound 5 was obtained as a white powder (35mg, 0.9 mmol). MS ESI m/e: 375 (M-H). ¹H NMR (500MHz) (CDCl₃) δ 7.65 (2H, d, J=8 Hz); 7.40-7.24 (5H, m); 6.96 (2H, d, J=8.5 Hz); 6.68 (1H, s); 4.88 (2H, s); 4.1 (1H, s); 2.77 (2H, m); 2.4 (3H, s); 1.86 (3H, s).

6.6 Example 6

[00187] The following compounds were prepared by methods similar to those described in Example 2.

TABLE 1

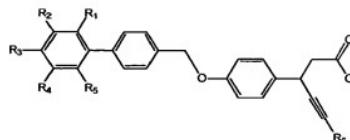


Compound	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
6.1	H	H	H	H	H	H
6.2	OC ₂ H ₅	H	H	H	H	H
6.3	H	H	OC ₂ H ₅	H	H	H
6.4	H	-OCH ₂ O-		H	H	H
6.5	H	H	CF ₃	H	H	H
6.6	H	CN	H	H	H	H
6.7	H	H	CN	H	H	H
6.8	CF ₃	H	H	H	H	H
6.9	H	CF ₃	H	H	H	H
6.10	H	H	OCF ₃	H	H	H
6.11	H	H	CF ₃	H	H	OC ₂ H ₅
6.12	OCH ₃	H	CF ₃	H	H	H

6.7 Example 7

[00188] The following compounds were prepared by methods similar to those described in Example 2.

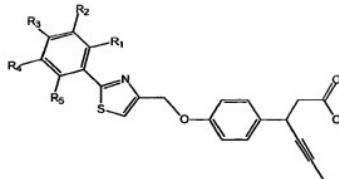
TABLE 2



Compound	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
7.1	H	H	H	H	H	H
7.2	CN	H	H	H	H	H
7.3	H	H	H	H	H	CH ₃
7.4	CN	H	H	H	H	CH ₃
7.5	OC ₂ H ₅	H	H	H	H	CH ₃
7.6	Cl	H	H	H	H	CH ₃
7.7	F	H	H	H	H	CH ₃
7.8	H	OC ₂ H ₅	H	H	H	CH ₃
7.9	H	H	OC ₂ H ₅	H	H	CH ₃
7.10	H	H	CF ₃	H	H	CH ₃
7.11	H	-OCH ₂ O-		H	H	CH ₃
7.12	OCH ₃	OCH ₃	H	H	H	CH ₃
7.13	H	OCH ₃	H	H	H	CH ₃
7.14	H	CN	H	H	H	CH ₃
7.15	H	H	CN	H	H	CH ₃

6.8 Example 8

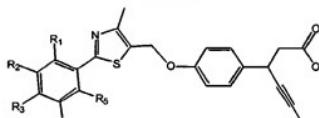
[00189] The following compounds were prepared by methods similar to those described in example 3.

TABLE 3

Compound	R ₁	R ₂	R ₃	R ₄	R ₅
8.1	H	H	CF ₃	H	H
8.2	H	H	H	H	H
8.3	H	H	Cl	H	H
8.4	H	H	OCH ₃	H	H
8.5	H	H	CH ₃	H	H
8.6	H	OCH ₃	OCH ₃	H	H
8.7	Cl	Cl	H	H	H

6.9 Example 9

[00190] The following compounds were prepared by methods similar to those described in Example 3.

TABLE 4

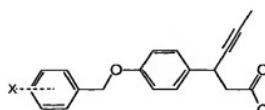
Compound	R ₁	R ₂	R ₃	R ₄	R ₅
9.1	H	H	CF ₃	H	H
9.2	H	H	CH ₃	H	H
9.3	H	H	H	H	H
9.4	H	OCH ₃	OCH ₃	H	H
9.5	H	H	Cl	H	H
9.6	Cl	H	H	H	H

6.10 Example 10

[00191] The following compounds were prepared by methods similar to those described in Examples 3-5. The carboxylic acids corresponding to 10.2 and 10.5 were

prepared according to the method of Huang et al. (*J. Amer. Chem. Soc.*; 2003, 22, 6653-6655) and Admas et al. (*Org. Synth.*; 1973, Coll. Vol. V; 107, 109.) respectively.

TABLE 5

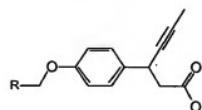


Compound	X	Compound	X
10.1	3-C(O)Ph	10.8	3-(2)-pyridyl
10.2	3-N(C ₂ H ₅)Ph	10.9	3-(3)-pyridyl
10.3	3-Phenoxy	10.10	3-(4)-pyridyl
10.4	4-C(O)Ph	10.11	4-(2)-pyridyl
10.5	4-SO ₂ Ph	10.12	4-(3)-pyridyl
10.6	4-CH ₂ Ph	10.13	4-(4)-pyridyl
10.7	4-C ₂ H ₄ PH	10.14	4-Pyrrol-1-yl

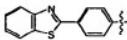
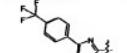
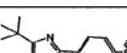
6.11 Example 11

[00192] The following compounds were prepared by methods similar to those described in Examples 3-5.

TABLE 6



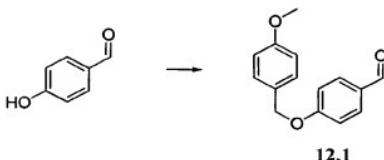
Compound	R
11.1	
11.2	
11.3	

Compound	R
11.4	
11.5	
11.6	
11.7	
11.8	

6.12 Example 12

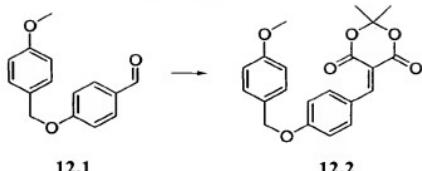
[00193] This example illustrates the preparation of (+/-)-3-(4-[4-methoxyphenyl)methoxy]- phenyl)-hex-4-ynoic acid.

Scheme 12.1



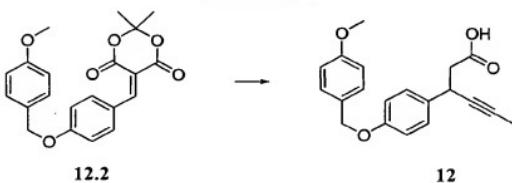
[00194] **4-[4-(4-methoxyphenyl)methoxy]benzaldehyde (12.1).** A 500mL round bottom flask was charged with 4-hydroxybenzaldehyde (40 g, 328 mmol) and DMF (250mL). 4-methoxybenzyl chloride (57.8mL, 426mmol) was added, followed by potassium carbonate (90g, 656mmol). The reaction mixture was stirred at room temperature for 5h then poured into ice water (2.5L). The product was collected by filtration and rinsed with water. After drying thoroughly, 78 g (98%) of aldehyde 12.1 was obtained as a light yellow powder. ¹H NMR(400MHz)(DMSO-*d*₆) δ 9.88 (s, 1H); 7.88 (d, 2H, *J*=8.7 Hz); 7.42 (d, 2H, *J*=8.8 Hz); 7.21 (d, 2H, *J*=8.8 Hz); 6.97 (d, 2H, *J*=8.6 Hz); 5.16 (s, 2H); 3.77 (s, 3H). MS ESI (pos.) m/e: 243.1 (M + H).

Scheme 12.2



[00195] **5-[{4-[(4-methoxyphenyl)methoxy]phenyl}methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (12.2).** Condensation with Meldrum's acid is carried out according to the procedure of DeWolf *et. al.* (*Biochemistry* 1989, 28, 3833-3842). A solution of Meldrum's acid (18g, 124mmol) compound 12.1 (30 g, 124 mmol) in toluene (100 mL) was treated with glacial acetic acid (4mL) and piperidine (2mL). The reaction mixture was stirred and heated at reflux until the removal of water with a Dean-Stark trap was complete. The reaction mixture was cooled to room temperature and the resulting solid was filtered and washed with cold toluene to yield 28g (62%) of 12.2 as a bright yellow powder.
¹H NMR(400MHz)(DMSO-*d*₆) δ 8.32 (s, 1H); 8.24 (d, 2H, *J*=8.9 Hz); 7.42 (d, 2H, *J*=8.6 Hz); 7.17 (d, 2H, *J*=9.0 Hz); 6.97 (d, 2H, *J*=8.7 Hz); 5.18 (s, 2H) 3.75 (s, 6H) 1.75 (s, 6H).

Scheme 12.3



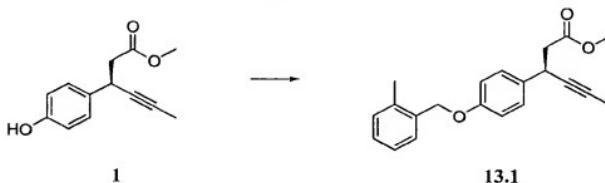
[00196] **(+/-)-3-(4-[(4-methoxyphenyl)methoxy]phenyl)-hex-4-yneoic acid (12).** To a stirring THF (120mL) solution of compound 12.2 (13.8g, 37.5mmol) under nitrogen was added 1-propynylmagnesium bromide in THF (0.5 N, 97.5mL) over a period of 20 minutes. After the addition was complete, the reaction mixture was stirred for 20 minutes, quenched with saturated aqueous NH₄Cl (50 mL) and extracted with ethyl acetate (3 x 50mL). The combined extracts were washed with water, dried over MgSO₄, filtered, and concentrated to a brown oil. A solution of this brown oil in 5:1 pyridine-water (360mL) was heated at 100 °C for 36h. The reaction mixture was cooled to room temperature and put in an ice-water bath. Concentrated HCl was carefully added to pH ~2. The resulting suspension was extracted with ethyl acetate (200mL x 3), dried over MgSO₄, filtered, and concentrated to an

off-white solid. Recrystallization from ethanol gave 9.5g (78%) of compound **12** as a white powder. ¹H NMR(500MHz)DMSO-*d*₆) δ 12.2 (s, 1H); 7.37 (d, 2H, *J*=8.5 Hz); 7.27 (d, 2H, *J*=8.5 Hz); 6.95 (d, 2H, *J*=8.0 Hz); 6.94 (d, 2H, *J*=8.5 Hz); 4.99 (s, 2H); 3.95 (m, 1H); 3.76 (s, 3H); 2.60 (m, 2H); 1.78 (d, 3H, *J*=1.5 Hz). MS ESI (neg.) m/e: 323.0 (M - 1).

6.13 Example 13

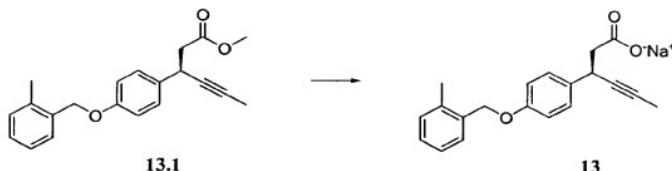
[00197] This example illustrates the preparation of (*3S*)-3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid sodium salt.

Scheme 13.1



[00198] **(3S)-3-[4-(2-Methyl-benzylxy)-phenyl]-hex-4-yneic acid methyl ester**
(13.1). 2-Methylbenzyl bromide (0.98 g, 5.3 mmol) and phenol **1** (0.97 g, 4.4 mmol) were dissolved in acetone (9 mL) and treated with Cs₂CO₃ (1.45 g, 4.4 mmol). The reaction was stirred at room temperature for 16 h then filtered and concentrated to an oil which was purified by radial chromatography (2 mm silica gel plate, 10% ethyl acetate in hexanes). Eluant containing compound **13.1** was concentrated to a colorless oil (1.37 g, 96%). This material was analyzed by chiral HPLC (Daicel ChiralPAK AD-H column, eluant: 0.1% TFA in 95:5 hexanes:2-propanol) and was found to have 94% ee. ¹H NMR(500MHz)(MeOH-d₄) δ 7.39 (d, 1H, *J*=7 Hz); 7.28 (d, 2H, *J*=8.5 Hz); 7.25-7.15 (m, 3H); 5.05 (s, 2H); 4.02 (m, 1H); 3.64 (s, 3H); 2.68 (m, 2H); 2.36 (s, 3H); 1.80 (d, 3H, *J*=2.5 Hz). MS ESI (pos.) m/e: 323.0 (M + H); 245.1 (M + Na).

Scheme 13.2

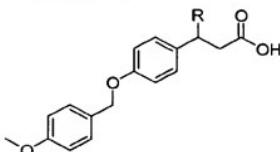


[00199] **(3*S*)-3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid sodium salt**
 (13). 2N KOH_(aq) (3.2 mL) was added to a solution of **13.1** (1.37 g, 4.25 mmol) in methanol (30 mL). The reaction was stirred at room temperature overnight and then taken up in copious water. The aqueous solution was adjusted to pH = 2.0 with 1N HCl_(aq) and extracted with ethyl acetate. The combined organic layers were washed with water, followed by brine. The solvent was removed under reduced pressure and the resulting residue dissolved in ethanol (4 mL) and treated with 1 equiv. of aqueous sodium bicarbonate. The solvents were removed under reduced pressure and the residue triturated with diethyl ether. After collecting by filtration and drying, sodium salt **13** (1.1 g) was obtained as a fine white powder. ¹H NMR(500MHz)(D₂O) δ 7.34-7.18 (m, 6H); 6.95 (d, 2H, *J*=6.5 Hz); 5.05 (s, 2H); 3.88 (m, 1H); 2.47 (d, 2H, *J*=8.5 Hz); 2.28 (s, 3H); 1.72 (d, 3H, *J*=2.5 Hz). MS ESI (pos.) m/e: 309.1 (M + H); 331.0 (M + Na). [α]_D = +20.6°.

6.14 Example 14

[00200] The following compounds were prepared using similar methods to those described in Example 12.

TABLE 7



Compound	R
14.1	Me ₃ Si— \equiv —{
14.2	F— C_6H_4 —{
14.3	Et
14.4	Me

Compound	R
14.5	
14.6	

6.15 Example 15

[00201] This example illustrates the preparation of *(3S)*-3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid.

Scheme 15.1



[00202] (+/-)-[4-(4-Methoxy-benzyloxy)-phenyl]-hex-4-yneoic acid ethyl ester (**15.1**). A 100 mL RB flask was charged with compound **12** (3.00 g, 9.25 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.67 g, 13.9 mmol), 4-dimethylaminopyridine (1.13 g, 9.25 mmol) and dichloromethane (30 mL), the mixture was stirred into a solution. After 15 min, ethyl alcohol (absolute, 1.00 mL) was added. After 2 h, the reaction was quenched with aqueous NaHCO₃ (sat., 100 mL). The layers were separated, and the organic layer was washed with aqueous NaHCO₃ (2 X 100 mL), dried over MgSO₄ and concentrated to a white powder (3.19 g, 98%) which was used without further purification.

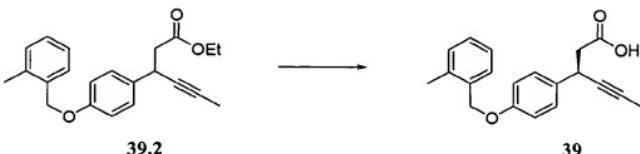
Scheme 15.2



[00203] (+/-)-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid ethyl ester (15.2).

Ester 15.1 (3.19 g, 9 mmol) was taken up in glacial acetic acid (100 mL) in a 250 mL RB Flask, and the suspension was heated to reflux for 16h. The solvent was removed under reduced pressure, and the residue was re-dissolved in ethyl acetate (200 mL). The solution was washed with 1 N HCl_(aq) (200 mL) and saturated brine (200 mL), dried over MgSO₄ and concentrated to a thick yellow oil, to which was added 2-methylbenzyl bromide (2.57 g, 13.9 mmol), cesium carbonate (6.03 g, 18.5 mmol) and DMF (20 mL). The suspension was heated to 80 °C for overnight. After cooling, the reaction was quenched with water (200 mL) and extracted with ethyl acetate (2 X 100 mL). The combined organic layers were washed with NaHCO₃ (sat. 2 X 100 mL), and NaCl (sat. 3 X 100 mL), dried over MgSO₄, and concentrated to a white powder (2.41 g, 79%).

Scheme 15.3



[00204] (3*S*)-3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid (15).

Compound 15.2 was dissolved in a mixture of 24 mL methanol and 24 mL isopropanol with the aid of sonication. The solution was filtered into a 50 mL glass vial. The racemic 39.2 was resolved with chiral normal phase HPLC using a ChiralTech AD semi-preparative column (2.0 cm X 25.0 cm), eluting isocratically with hexane/isopropanol (92:8) at a flow rate 20 mL/min. Each injection contained 50 mg of ester 15 (1 mL). The absorbance at 220 nm was used for detection. Both enantiomers were collected. After 36 injections, the separated enantiomers were dried to give white solids. Analytical chiral HPLC (Chiralttech AD-H column, 0.4 cm X 25.0 cm, 8% isopropanol/hexane, 1 mL/min) indicated both compounds were optically pure. The enantiomers were referred to as A (retention time = 11.5 min) and B (retention time = 15.6 min).

[00205] A RB flask was charged with enantiomer A (0.65 g), ethanol (10 mL) and 2N KOH (10 mL). and was stirred for 2 h at room temperature. After acidification to pH~2 with citric acid, the product was extracted into ethyl acetate (100 mL). The organic layers were washed with saturated brine(2 X 50 mL), dried over MgSO₄ and concentrated to a

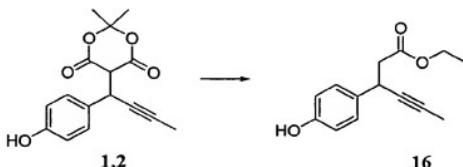
yellow oil (0.59 g, 42% overall). An aliquot (12.0 mg) was made into a 1 mL DMF solution, and optical rotation was measured. This enantiomer was assigned to (*S*) according to DeWolf Jr. et al. (*Biochemistry*, 1989, 28, 3833-3842).

[00206] ^1H NMR (400 MHz, acetone- d_6) δ 7.45 (d, 1H, $J=7.15$ Hz); 7.37 (d, 2H, $J=8.66$ Hz); 7.25 (d, 1H, $J=1.42$ Hz); 7.24 (m, 2H); 7.00 (d, 2H, $J=8.74$ Hz); 5.11 (s, 2H); 4.05 (m, 1H); 2.70 (m, 2H); 2.39 (s, 3H); 2.10 (s, 1H); 1.80 (d, 3H, $J=2.41$). MS-ESI (neg.) m/e: 307.1 (M-H); 637.2 (2M-H). $[\alpha]_D^{20}$: +16.32 (c1.2, DMF).

6.16 Example 16

[00207] This example illustrates the preparation of 3-(4-Hydroxy-phenyl)-hex-4-yneoic acid ethyl ester.

Scheme 16.1



[00208] **3-(4-Hydroxy-phenyl)-hex-4-yneoic acid ethyl ester (16).** Phenol 1.2 (1.2 g, 4 mmol) was dissolved in pyridine (3 mL) and ethanol (1 mL). The mixture was heated to 90 °C for 16h and then concentrated to an oil which was purified by column chromatography (elution with 1-3% MeOH in dichloromethane). Phenol 16 (0.88 g, 91%) was obtained as an oil. ^1H NMR(500MHz)(acetone- d_6) δ 8.24 (s, 1H); 7.21 (d, 2H, $J=9.5$ Hz); 6.78 (d, 2H, $J=9.0$ Hz); 4.06 (m, 2H); 3.98 (m, 1H); 2.68-2.59 (m, 2H); 1.78 (d, 3H, $J=2.5$ Hz); 1.75 (t, 3H, $J=7.0$ Hz). MS ESI (pos.) m/e: 233.1 (M + H); 255.1 (M + Na).

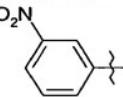
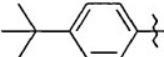
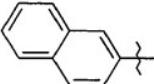
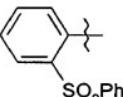
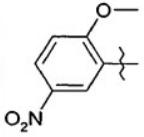
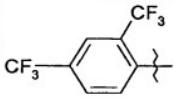
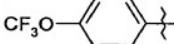
6.17 Example 17

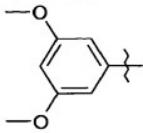
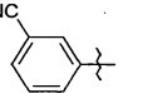
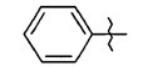
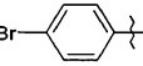
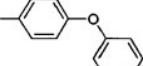
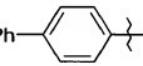
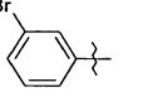
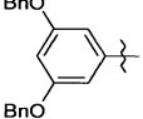
[00209] The following compounds were prepared by methods similar to those of examples 12 and 15.

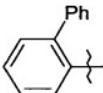
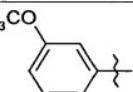
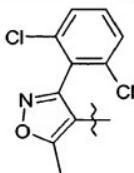
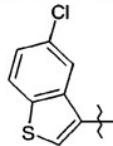
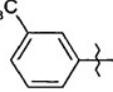
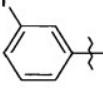
TABLE 8

Compound	R
17.1	
17.2	
17.3	
17.4	
17.5	
17.6	
17.7	

Compound	R
17.8	
17.9	
17.10	
17.11	
17.12	
17.13	
17.14	
17.15	
17.16	

Compound	R
17.17	
17.18	
17.19	
17.20	
17.21	
17.22	
17.23	
17.24	

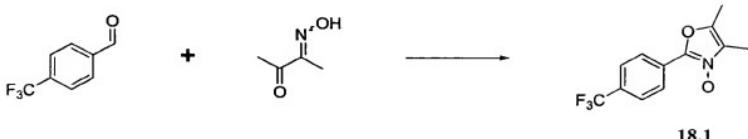
Compound	R
17.25	
17.26	
17.27	
17.28	
17.29	
17.30	
17.32	
17.33	

Compound	R
17.34	
17.35	
17.36	
17.37	
17.38	
17.39	
17.40	

6.18 Example 18

[00210] This example illustrates the preparation of 3-{4-[5-Methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid.

Scheme 18.1



[00211] **4,5-dimethyl-2-(4-trifluoromethyl-phenyl)-oxazole-3-oxide (18.1).** A 100 mL pear-shaped flask was charged with butane-2,3-dione monooxime (2.1 g, 20.4 mmol), 4-(trifluoromethyl)benzaldehyde (3.0 mL, 22.4 mmol), and acetic acid (20 mL). The mixture was cooled to 0° C. A solution of 4N HCl in dioxane (7.0 mL, 28.0 mmol) was added dropwise to the reaction and the resultant mixture was stirred at 0° C for 20 minutes. Diethyl ether (30 mL) was added to the reaction and the mixture was allowed to warm to room temperature overnight. The solvent was removed under reduced pressure and the resulting residue was taken up in water (300 mL). Conc. NH₄OH_(aq) was added to adjust the pH to 9.0. The mixture was extracted with ethyl acetate (2 x 75 mL), and the combined organic layers were washed with water (100 mL), followed by saturated brine (100 mL). The organic layer was dried (Na₂SO₄) and the solvent removed under reduced pressure. The resulting residue was purified via radial chromatography (3% MeOH in DCM) to yield 1.8 g (35%) of 4,5-dimethyl-2-(4-trifluoromethyl-phenyl)-oxazole-3-oxide as a white solid. LC/MSD *m/e*: 258.1 (M+H); ¹H NMR (400 MHz) (Acetone-*d*₆) δ 8.68 (d, 2H, *J*=8.0 Hz), 7.89 (d, 2H, *J*=8.0 Hz), 2.45 (s, 3H), 2.16 (s, 3H).

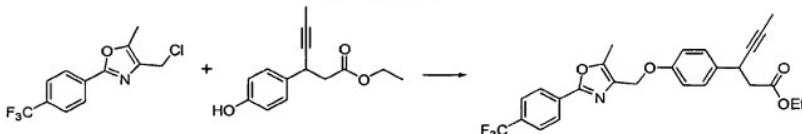
Scheme 18.2



[00212] **4-chloromethyl-5-methyl-2-(4-trifluoromethyl-phenyl)-oxazole (18.2).** Phosphorous oxychloride (0.72 mL, 7.8 mmol) was added dropwise (exothermic!) to an oven-dried 100 mL pear-shaped flask charged with 18.1 (1.8 g, 7.00 mmol) and dichloromethane (20 mL). The reaction was refluxed under nitrogen atmosphere for 30 minutes and then cooled to room temperature. The reaction was washed with water (2 x

250 mL) and the combined aqueous layers were back extracted with DCM (2 x 25 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting residue was purified via radial chromatography (15% diethyl ether in hexanes) to yield 216 mg (15%) of 4-chloromethyl-5-methyl-2-(4-trifluoromethyl-phenyl)-oxazole as a white solid. LC/MSD *m/e*: 276.0 (M+H); ^1H NMR (400 MHz) (CDCl_3) δ 8.15 (2H, d, *J*=8.0 Hz), 7.73 (2H, d, *J*=8.0 Hz), 4.59 (2H, s), 2.48 (2H, s).

Scheme 18.3



18.2

16

18.3

[00213] **3-{4-[5-Methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-yneoic acid ethyl ester (18.3).** Cesium carbonate (0.51 g, 1.57 mmol) was added to a solution of **18.2** (216 mg, 0.79 mmol) and phenol **16** (220 mg, 0.79 mmol) in DMF (8 mL). The reaction was stirred at room temperature overnight and then taken up in water (500 mL). The solution was adjusted to pH = 4.0 with 1N HCl(aq) and extracted with ethyl acetate (2 x 25 mL). The combined organics were washed with water, followed by brine. The solvent was removed under reduced pressure and the resulting residue was purified via radial chromatography (20% diethyl ether in hexanes) to yield 304 mg (82%) of **3-{4-[5-Methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-yneoic acid ethyl ester.** LC/MSD *m/e*: 472.0 (M+H); ^1H NMR (400 MHz) (CDCl_3) δ 8.16 (2H, d, *J*=8.0 Hz), 7.73 (2H, d, *J*=8.0 Hz), 7.33 (2H, m), 6.99 (2H, m), 5.01 (2H, s), 4.14 (3H, m), 2.72 (2H, m), 2.48 (3H, s), 1.85 (3H, s), 1.26 (3H, t, *J*=8.0 Hz).

Scheme 18.4



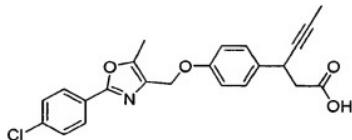
18.3

18

[00214] 3-{4-[5-Methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-yneoic acid (**18**). 2N KOH_(aq) was added to a solution of **18.3** (304 mg, 0.65 mmol) in ethanol (5 mL). The reaction was stirred at room temperature overnight and then taken up in copious water. The aqueous solution was adjusted to pH = 2.0 with 1N HCl_(aq) and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with water, followed by brine. The solvent was removed under reduced pressure and the resulting residue was purified via radial chromatography (40% ethyl acetate in Hexanes + 0.1% AcOH) to yield 150 mg (52%) of compound **18** as a glass. LC/MSD *m/e*: 444.0 (M+H); ¹H NMR (400 MHz) (acetone) δ 8.21 (2H, m), 7.89 (2H, d, *J*=8.0 Hz), 7.38 (2H, m), 7.03 (2H, m), 5.06 (2H, s), 4.06 (1H, m), 2.70 (2H, m), 2.52 (3H, s), 1.81 (3H, s).

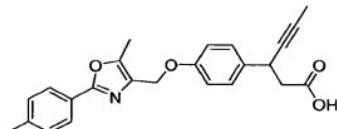
6.19 Example 19

[00215] Examples 19-22 were prepared using methods similar to those described in Example **18**.



[00216] 3-{4-[5-Methyl-2-(4-chloro-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-yneoic acid (**19**). LC/MSD *m/e*: 410.0 (M+H). ¹H-NMR (400 MHz) (acetone-*d*₆) δ 8.02 (2H, m), 7.49 (2H, m), 7.35 (2H, m), 7.01 (2H, m), 5.04 (2H, s), 4.09 (1H, m), 2.77 (2H, m), 2.48 (3H, s), 1.86 (3H, s).

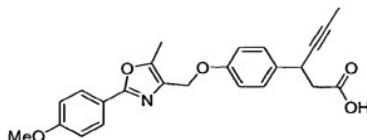
6.20 Example 20



[00217] 3-{4-[5-Methyl-2-(4-methyl-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-yneoic acid (**16**). LC/MSD *m/e*: 390.2 (M+H). ¹H NMR (400 MHz) (CDCl₃) δ 7.96 (2H,

m), 7.34 (2H, m), 6.70 (2H, m), 5.02 (2H, s), 4.09 (1H, m), 2.80 (2H, m), 2.47 (3H, s), 1.85 (3H, s).

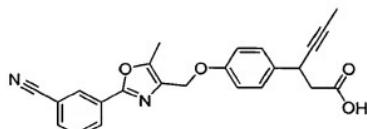
6.21 Example 21



21

[00218] 3-{4-[5-Methyl-2-(4-methoxy-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid (21). LC/MSD *m/e*: 406.1 (M+H). ^1H NMR (400 MHz) (acetone- d_6) δ 7.89 (2H, d, *J*=9.0 Hz) 7.30 (2H, m), 7.09 (2H, d, *J*=9.0 Hz), 7.00 (2H, m), 4.97 (3H, s), 3.90 (1H, m), 3.84 (3H, s), 2.44 (3H, s), 1.79 (3H, s).

6.22 Example 22



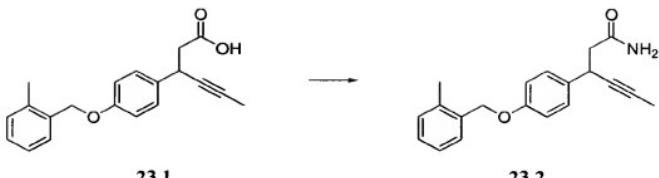
22

[00219] 3-{4-[5-Methyl-2-(3-cyano-phenyl)-oxazol-4-ylmethoxy]-phenyl}-hex-4-ynoic acid (22). LC/MSD *m/e*: 401.2 (M+H). ^1H NMR (400 MHz) (acetone- d_6) δ 8.33 (2H, m), 7.91 (1H, m), 7.79 (1H, m), 7.38 (2H, m), 7.08 (2H, m), 5.06 (2H, s), 4.06 (1H, m), 2.70 (2H, m), 2.51 (3H, s), 1.81 (3H, s).

6.23 Example 23

[00220] The following example illustrates the synthesis of 5-{2-[4-(2-Methylbenzyloxy)-phenyl]-pent-3-ynyl}-1*H*-tetrazole.

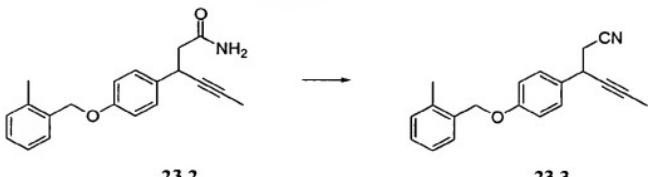
Scheme 23.1



[0022-1] 3-[4-(2-Methyl-benzyl-oxy)-phenyl]-hex-4-yneoic acid amide (23-2).

Carbonyl diimidazole (0.46 g, 2.84 mmol) was added to a solution of 3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid (See Example 13) (0.73 g, 2.37 mmol) in anhydrous THF (10 mL). The mixture was stirred at room temperature for 2 hours. Conc. NH₄OH (10 mL) was then added to the mixture, and the reaction was stirred at room temperature overnight. The reaction mixture was poured into water (300 mL) and the solution was adjusted to pH = 7 with conc. HCl. The aqueous layer was then extracted with 3 x 25 mL ethyl acetate. The combined organic layers were washed with water, followed by brine. The organic layer was then dried (Na₂SO₄) and concentrated under reduced pressure to yield 0.48 g (70%) of 3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-ynoic acid amide (**23.2**) as a light yellow solid. LC/MSD *m/e*: 308.4 (M+H)

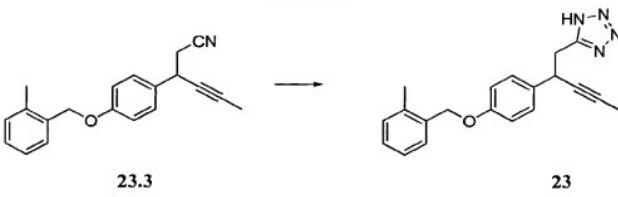
Scheme 23.2



[00222] 3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-yenenitrile (23.3). An oven-dried 50 mL round-bottomed flask was charged with DMF (8 mL) and a stir bar. The solution was cooled to 0 °C in an ice bath. Thionyl chloride (160 μ L, 1.0 mmol) was added slowly via syringe. The mixture was stirred at 0 °C for an additional 45 minutes. Nitrile 23.2 (300 mg, 0.98 mmol) was then added to the mixture as a solution in DMF (2 mL). The reaction was stirred at 0 °C for an hour, and was then allowed to gradually warm to room temperature overnight. The reaction mixture was partitioned between ice water and ethyl acetate. The aqueous layer was extracted 2 additional times with 25 mL ethyl acetate. Sat. NaHCO₃ was then added to the aqueous layer and the aqueous layer was extracted a third time with ethyl acetate. The combined organic layers were washed with sat. NaHCO₃ and

concentrated under reduced pressure. The resulting residue was purified via radial chromatography (15% ethyl acetate in hexanes) to yield 203 mg (72%) of 3-[4-(2-Methyl-benzyloxy)-phenyl]-hex-4-yenitrile (23.3). ^1H NMR (400 MHz) (acetone- d_6) δ 7.44 (3H, m), 7.24 (3H, m), 7.05 (2H, m), 5.13 (2H, s), 4.09 (1H, m), 2.89 (2H, m), 2.39 (3H, s), 1.88 (3H, s).

Scheme 23.4

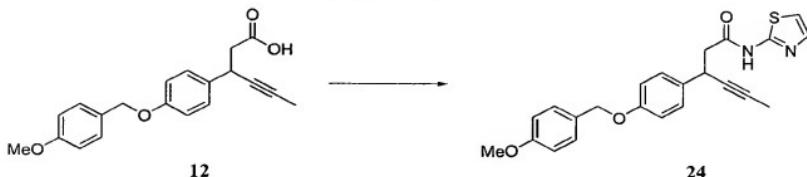


[00223] 5-[2-[4-(2-Methyl-benzylxy)-phenyl]-pent-3-ynyl]-1*H*-tetrazole (23). To a solution of 23.3 (200 mg, 0.51 mmol) in DMF (5 mL) was added sodium azide (35 mg, 0.54 mmol) and ammonium chloride (29 mg, 0.54 mmol). The solution was stirred at 110° C for 48 hours. The reaction mixture was poured into 50 mL of water and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were concentrated under reduced pressure, and the resulting residue was purified via HPLC to yield 5 mg (3%) of 5-[2-[4-(2-Methyl-benzylxy)-phenyl]-pent-3-ynyl]-1*H*-tetrazole (23) as a film. LC/MSD *m/e*: 333.1 (M+H). ¹H NMR (400 MHz) (acetone-*d*₆) δ 7.45 (1H, m), 7.34 (2H, m), 7.25 (3H, m), 7.00 (2H, m), 5.11 (2H, s), 4.17 (1H, m), 3.37 (2H, d, *J*=7 Hz), 2.39 (3H, s), 1.79 (3H, s).

6.24 Example 24

[00224] The following example illustrates the synthesis of 3-[4-(4-Methoxy-benzyloxy)-phenyl]-hex-4-ynoic acid thiazol-2-ylamide.

Scheme 24.1



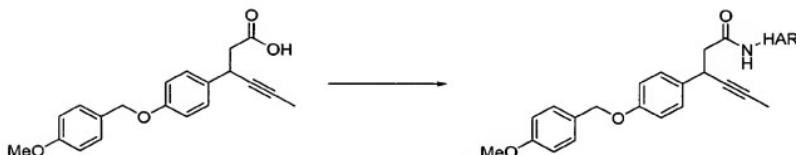
[00225] 3-[4-(4-Methoxy-benzyl)-phenyl]-hex-4-ynoic acid thiazol-2-ylamide (24). A pear-shaped flask was charged with a stir bar, compound 12 (50 mg, 0.154 mmol), carbonyl diimidazole (25 mg, 0.154 mmol) and THF (4 mL). The mixture was refluxed for

1 hour, and 2-amino thiazole (16 mg, 0.154 mmol) was then added. The reaction was refluxed for 48 hours, poured into water and extracted with ethyl acetate. The organic layer was concentrated and the resulting residue was purified via HPLC to yield 1.0 mg (2%) of 3-[4-(4-Methoxy-benzyl)-phenyl]-hex-4-ynoic acid thiazol-2-ylamide (24) as a film. ¹H NMR (400 MHz) (acetone-*d*₆) δ 7.39 (4H, m), 7.11 (1H, s), 6.95 (3H, m), 5.03 (2H, s), 3.82 (3H, s), 2.95 (2H, m), 1.79 (3H, s).

6.25 Example 25

[00226] The compounds in the following table were prepared using the method described in Example 24.

Scheme 25.1

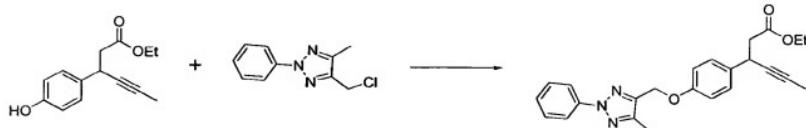


Compound	HAR
25.1	Tetrazole-5-yl
25.2	pyrimidin-2-yl
25.3	Pyridin-2-yl

6.26 Example 26

[00227] The following example illustrates the preparation of 3-[4-(5-Methyl-2-phenyl-2*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-hex-4-ynoic acid (26).

Scheme 26.1



17

26.1

26.2

[00228] 3-[4-(5-Methyl-2-phenyl-2*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-hex-4-ynoic acid ethyl ester (**26.2**). Cesium carbonate (107 mg, 0.33 mmol) was added to a solution of **16** (60 mg, 0.22 mmol) in DMF (5 mL). The mixture was stirred at room temperature for 5 minutes, and 4-Chloromethyl-5-methyl-2-phenyl-2*H*-[1,2,3]triazole (55 mg, 0.22 mmol) was added. The reaction was heated to 60° C and stirred overnight. The reaction mixture was then poured into copious water. 1N HCl_(aq) was added to adjust the pH to 4.0. The aqueous layer was extracted with ethyl acetate. The organic layer was then washed with water, followed with brine. The organic layer was dried (Na₂SO₄) and concentrated. The resulting residue was purified via radial chromatography (20% ethyl acetate in hexanes) to yield 60 mg (66%) of 3-[4-(5-Methyl-2-phenyl-2*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-hex-4-ynoic acid ethyl ester (**26.2**). LC/MSD *m/e*: 404.2 (M+H).



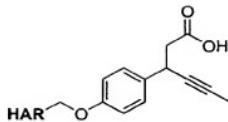
26.2

26

[00229] 3-[4-(5-Methyl-2-phenyl-2*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-hex-4-ynoic acid (**26**). 2N KOH(aq) (1 mL) was added to a solution of 9.1 (68 mg, 0.17 mmol) in EtOH (2 mL). The reaction was stirred at room temperature overnight and then poured into water. The aqueous mixture was acidified to pH = 2 with 1N HCl(aq), and then extracted with ethyl acetate. The organic layer was washed with water, followed by brine. The organic layer was then concentrated under reduced pressure and the resulting residue was purified via radial chromatography (20% ethyl acetate in hexanes) to yield 60.3 mg (95%) of compound **26** as a colorless oil. LC/MSD *m/e*: 374.0 (M-H); ¹H NMR (400 MHz) (acetone-*d*₆) δ 8.05 (2H, d, *J*=8.0 Hz), 7.56 (2H, t, *J*=8.0 Hz), 7.40 (3H, t, *J*=8.0 Hz), 7.06 (2H, d, *J*=8.0 Hz), 5.28 (2H, s), 4.05 (1H, m), 2.70 (2H, m), 2.44 (3H, s), 1.80 (3H, s).

6.27 Example 27

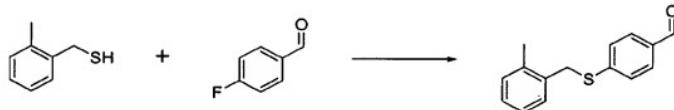
[00230] The compounds in the following table were prepared using methods similar to those described in Example **26**.



Compound	HAR
26.1	
26.2	
26.3	

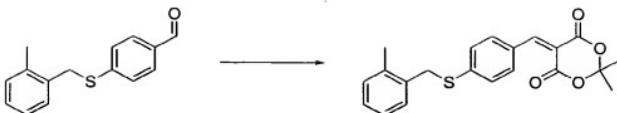
6.28 Example 28

[00231] The following example illustrates the preparation of 3-[4-(2-Methyl-benzylsulfanyl)-phenyl]-hex-4-yneoic acid (28).



28.1

[00232] **4-(2-Methyl-benzylsulfanyl)-benzaldehyde (28.1).** 4-fluoro-benzaldehyde (1.16 g, 9.32 mmol) was added dropwise over 2 minutes to a solution of *o*-tolyl-methanethiol (1.35 g, 9.79 mmol) and Cesium carbonate (3.19 g, 9.79 mmol) in DMF (20 mL). The solution was stirred at 40 °C overnight and then poured into copious water. The pH of the solution was adjusted to 4 with 1N HCl_(aq), and the aqueous solution was extracted with ethyl acetate (2 x 35 mL). The combined organic layers were washed with water, followed by brine. The combined organic layers were then dried (Na₂SO₄) and the solvent removed under reduced pressure. The resulting residue was purified via radial chromatography (15% ethyl acetate in hexanes) to yield 1.29 g (54%) of 4-(2-Methyl-benzylsulfanyl)-benzaldehyde (28.1). LC/MSD *m/e*: 243.0 (M+H).



28.1

28.2

[00233] **2,2-Dimethyl-5-[4-(2-methyl-benzylsulfanyl)-benzylidene]-[1,3]dioxane-4,6-dione (28.2).**

Pyrrolidine (0.45 mL, 5.27 mmol) was added to a solution of aldehyde 28.1 in diethyl ether (20 mL) and the mixture was sonicated for 5 minutes. The mixture was then added to a solution of Meldrum's acid (0.73 g, 5.08 mmol) in diethyl ether (20 mL) and the resultant mixture was sonicated for 5 minutes, forming a solid. The solid was filtered, rinsed with diethyl ether, and then suspended in DCM (10 mL). p-Toluenesulfonic acid (0.97 g, 5.10 mmol) was then added to the suspension and the suspension was sonicated until clear. The solvent was removed under reduced pressure, and the resulting residue was taken up in diethyl ether and partitioned between water and ethyl acetate. The aqueous layer was extracted 2 additional times with ethyl acetate. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to yield 1.05 g (54%) of 2,2-Dimethyl-5-[4-(2-methyl-benzylsulfanyl)-benzylidene]-[1,3]dioxane-4,6-dione (28.2) as a yellow oil. The resulting yellow oil was used without further purification. LC/MSD *m/e*: 391.1 (M+Na).



28.2

28.3

[00234] **2,2-Dimethyl-5-{1-[4-(2-methyl-benzylsulfanyl)-phenyl]-but-2-ynyl}-[1,3]dioxane-4,6-dione (28.3).**

An oven-dried 100 mL pear-shaped flask, fitted with an oven-dried stir bar, was charged with a 0.5 M solution of 1-propynyl magnesium bromide in THF (12.5 mL, 6.27 mmol) via cannula. The solution was cooled to 0° C, and then a solution of 28.2 (1.05 g, 2.85 mmol) in anhydrous THF (6 mL) was added over 3 minutes via cannula. The reaction was stirred at 0° C for 5 minutes and then stirred at room temperature for 1.5 hours. The reaction mixture was poured into sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ and extracted with ethyl acetate. The combined organic layers were washed with water,

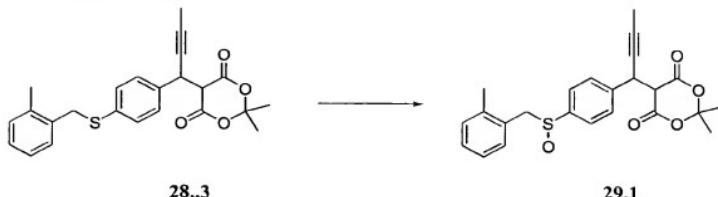
followed by brine. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified via radial chromatography (20% ethyl acetate in hexanes) followed by recrystallization from hot ethyl acetate and hexanes to yield 162 mg (15%) of 2,2-Dimethyl-5-[1-[4-(2-methyl-benzylsulfanyl)-phenyl]-but-2-ynyl]-[1,3]dioxane-4,6-dione (28.3). LC/MSD *m/e*: 409.1 ($\text{M}+\text{H}$).



[00235] 3-[4-(2-Methyl-benzylsulfanyl)-phenyl]-hex-4-yneic acid (28). A solution of 28.3 (20 mg, 0.05 mmol) in 5:1 pyridine:water (6 mL) was heated to 80 °C for 72 hours. The reaction was poured into 500 mL of water and the solution was acidified with 1N HCl_(aq) (65 mL). The aqueous solution was extracted with ethyl acetate and the combined organic layers were washed with water, followed by brine. The combined organic layers were then dried (Na₂SO₄) and concentrated *in vacuo*. The resultant residue was then purified via radial chromatography (30% ethyl acetate in hexanes) to yield 18 mg (quantitative) 3-[4-(2-Methyl-benzylsulfanyl)-phenyl]-hex-4-yneic acid (28). LC/MSD *m/e*: 323.1 (M-H).

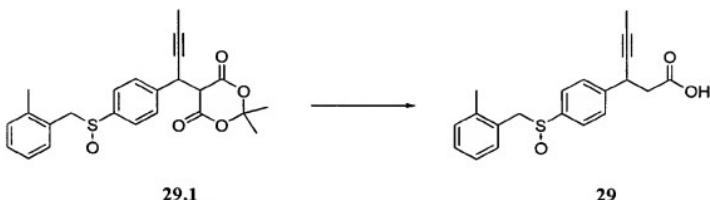
6.29 Example 29

[00236] The following example illustrates the preparation of 3-(4-*o*-Tolylmethanesulfinyl-phenyl)-hex-4-ynoic acid.



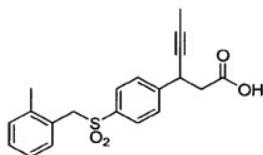
[00237] 2,2-Dimethyl-5-[1-(4-*o*-tolylmethanesulfinyl-phenyl)-but-2-ynyl]-[1,3]dioxane-4,6-dione (29.1). Hydrogen peroxide (20 μ L, 0.05 mmol) was added to a 0°C

solution of 28.3 (20 mg, 0.05 mmol) in AcOH (2 mL). The reaction was stirred at 80°C for 1.5 hours, then cooled to room temperature and stirred for 16 hours. The reaction mixture was poured into cold water and the resulting solution was acidified to pH = 2 with 6N HCl(aq). The aqueous layer was extracted with ethyl acetate and *sec*-butanol. The combined organic layers were concentrated to yield 10 mg (50%) of 2,2-Dimethyl-5-[1-(4-*o*-tolylmethanesulfinyl-phenyl)-but-2-ynyl]-[1,3]dioxane-4,6-dione (29.1). LC/MSD *m/e*: 383.0 (consistent with di-acid -H).



[00238] 3-(4-*o*-Tolylmethanesulfinyl-phenyl)-hex-4-ynoic acid (29). 29.1 (10.0 mg, 0.025 mmol) was hydrolyzed using the methods described in Example 28 to yield 3.0 mg (25%) of 3-(4-*o*-Tolylmethanesulfinyl-phenyl)-hex-4-ynoic acid (29). LC/MSD *m/e*: 339.1 (M-H), ¹H NMR (400MHz) (acetone-*d*₆) δ 7.60 (2H, m), 7.49 (2H, m), 7.21 (2H, m), 7.04 (2H, m), 5.63 (2H, s), 4.17 (1H, m), 2.81 (2H, m), 2.22 (3H, s), 1.88 (3H, s).

6.30 Example 30



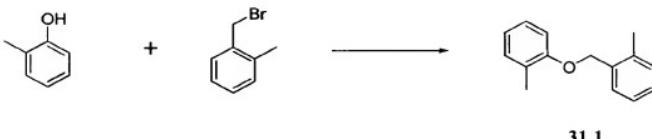
30

[00239] 3-(4-*o*-Tolylmethanesulfonyl-phenyl)-hex-4-ynoic acid (30) was prepared using methods similar to those described in Example 29. LC/MSD *m/e*: 357.2 (M+H); ¹H NMR (400MHz) (acetone-*d*₆) δ 7.69 (3H, m), 7.50 (1H, m), 7.17 (4H, m), 4.53 (2H, s), 4.22 (1H, m), 2.79 (2H, m), 2.27 (3H, s), 1.82 (3H, s).

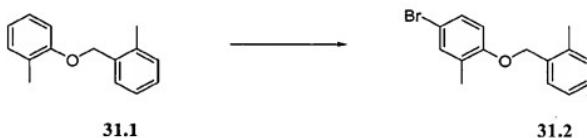
6.31 Example 31

[00240]

The following example illustrates the preparation of 3-[2-Methyl-4-phenyl-hex-4-enoic acid (31).



[00241] **2-(2-methyl-benzyl)benzyl ether (31.1).** α -bromo- α -xylene (2.0 g, 10.81 mmol) was added to a solution of 2-methyl-phenol (1.06 g, 9.82 mmol) and cesium carbonate (7.99 g, 24.55 mmol) in DMF (20 mL). The reaction was stirred at 80° C overnight. The reaction mixture was acidified with 25 mL 1N HCl(aq) and poured into copious water. The aqueous layer was extracted with ethyl acetate and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified via radial chromatography (20% ethyl acetate in hexanes) to yield 1.82 g (88%) of 2-(2-methyl-benzyl)benzyl ether (31.1). LC/MSD *m/e*: 213.2 ($\text{M}+\text{H}$).

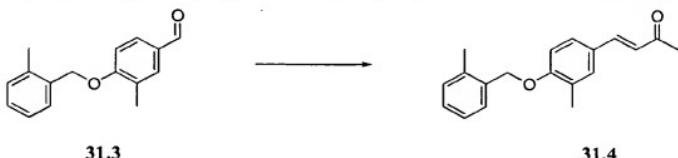


[00242] **2-(2-methyl-benzylxy)-5-bromotoluene (31.2).** NBS (1.46 g, 8.23 mmol) was added to a solution of 31.1 (1.59 g, 7.48 mmol) in carbon tetrachloride (8 mL). The reaction was stirred at 60° C overnight and filtered to remove succinimide. The filtrate was concentrated *in vacuo* and purified via radial chromatography (15% diethyl ether in hexanes) to yield 0.65g (25%) of 2-(2-methyl-benzylxy)-5-bromotoluene (31.2). LC/MSD m/e: 314.2 (M+Na).



[00243] **2-Methyl-4-(2-methyl-benzyloxy)-benzaldehyde** (31.3). A 2.5M solution of *n*-BuLi (2.1 mL, 5.26 mmol) in THF was added dropwise to a -78° C solution of 31.2 (1.46 g, 5.01 mmol) in THF (25 mL). The reaction was stirred at -78° C for 15 minutes and

then DMF (3.3 mL) was added. Cooling was removed after 5 minutes and the reaction was allowed to warm to room temperature. The reaction was partitioned between ethyl acetate and water and the aqueous layer was extracted 1 additional time with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. The resulting residue was purified via radial chromatography (5% ethyl acetate in hexanes) to yield 269 mg (22%) of 2-Methyl-4-(2-methyl-benzoyloxy)-benzaldehyde (31.3). LC/MSD m/e : 241.2 ($\text{M}+\text{H}$).



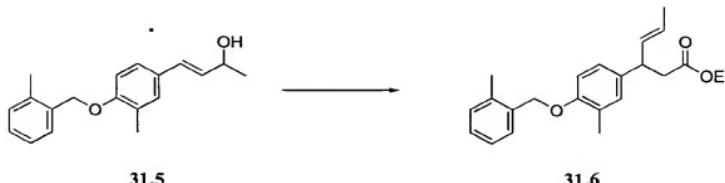
[00244] 4-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-but-3-en-2-one (31.4). 2N NaOH_(aq) (0.6 mL) was added to a solution of 31.3 (100 mg, 0.42 mmol) in acetone (1 mL). The reaction was stirred at room temperature overnight and then taken up in water. The aqueous solution was acidified with 1N HCl_(aq) (1.5 mL) and extracted with ethyl acetate. The organic extracts were washed with brine, dried (Na₂SO₄), and concentrated *in vacuo*. The resultant residue was purified via radial chromatography (20% ethyl acetate in hexanes) to yield 74 mg (63%) of 4-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-but-3-en-2-one (31.4). LC/MSD *m/e*: 281.4 (M+H); ¹H NMR (400 MHz) (acetone-*d*₆) δ 7.83 (1H, d, *J*=16), 7.70 (1H, m), 7.46 (1H, m), 7.25 (3H, m), 6.96 (2H, m), 6.63 (1H, d, *J*=16 Hz).



[00245] 4-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-but-3-en-2-ol (31.5).

NaBH_4 (20 mg, 0.51 mmol) was added to a 0.4 M solution of CeCl_3 in MeOH (0.65 mL, 0.26 mmol), 31.4 (74 mg, 0.26 mmol), and THF (1 mL). The reaction was stirred, uncapped, until gas evolution ceased. The reaction was quenched with water (1.5 mL) and partitioned between water and diethyl ether. The aqueous layer was extracted 2 times with diethyl ether and the combined organic layers were washed with brine and concentrated *in*

vacuo to yield 69 mg (93%) of 4-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-but-3-en-2-ol (31.5). LC/MSD *m/e*: 266.3 (M-OH); ¹H NMR (400 MHz) (DMSO-*d*₆) δ 7.44 (2H, m), 7.25 (3H, m0, 6.86 (2H, m), 6.75 (1H, m), 6.08 (1H, m), 5.11 (2H, s), 4.40, (1H, m), 2.38 (3H, s), 2.32 (3H, s), 1.29 (3H, m).



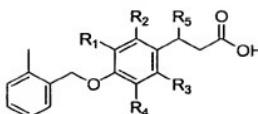
[00246] 3-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-hex-4-enoic acid ethyl ester (31.6). Propionic acid (cat.) was added to a solution of 31.5 (69 mg, 0.24 mmol) in 1,1,1-triethoxy-ethane (440 μ L, 2.4 mmol). The reaction was stirred at 105 °C overnight. The solvent was removed under reduced pressure and the resulting residue was purified via radial chromatography (5% ethyl acetate in hexanes) to yield 33 mg (39%) of 3-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-hex-4-enoic acid ethyl ester (31.6). LC/MSD *m/e*: 375.0 (M+Na).



[00247] 3-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-hex-4-enoic acid (31). The hydrolysis of 31.6 (33 mg, 0.094 mmol) was carried out using methods similar to those described in Example 26 to yield 5.7 mg (19%) of 3-[2-Methyl-4-(2-methyl-benzyloxy)-phenyl]-hex-4-enoic acid (31). ^1H NMR (400 MHz) (acetone) δ 7.44 (2H, m), 7.25 (3H, m), 6.86 (2H, m), 6.73 (1H, m), 6.10 (1H, m), 5.64 (2H, s), 4.42 (1H, m), 2.38 (3H, s), 2.32 (3H, s), 1.29 (3H, d, $J=7.0$ Hz).

6.32 Example 32

[00248] The following compounds were made using methods similar to those described in Examples 28 and 31.

TABLE 9

Compound	R1	R2	R3	R4	R5
32.1	Me	H	Me	H	
32.2	H	Ph	H	H	
32.3	Me	Me	H	H	
32.4	Ph	H	H	H	

6.33 Example 33

[00249] The following example illustrates the preparation 3-[4-(3-Methoxybenzyloxy)-phenyl]-5-methyl-hex-4-enoic acid (33).



33.1

[00250] **2-[4-(3-Methoxy-benzyloxy)-benzylidene]-malonic acid dimethyl ester (33.1).** K_2CO_3 was added to a solution of 4-hydroxybenzylidene-malonic acid dimethyl ester (6.95 mmol) and 4-methoxybenzyl chloride (7.64 mmol) in DMF (15 ml). It was stirred at room temperature overnight. The reaction was poured into water, and the product was extracted with ethyl acetate twice. The organic layer was washed with water and saturated brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting residue was purified using silica gel column chromatography (hexane/ethyl acetate = 2/1) to give compound 33.1 as a white solid (3.2 mmol).



33.1

33.2

[00251] 2-{1-[4-(3-Methoxy-benzyloxy)-phenyl]-3-methyl-but-2-enyl}-malonic acid dimethyl ester (33.2). 2-methyl-1-propenylmagnesium bromide (3 mL, 0.5 M in THF) was added dropwise to a solution of compound 33.1 (1.0 mmol) in THF. The reaction mixture was stirred at room temperature for 1hr and then quenched with saturated NH₄Cl_(aq) and the aqueous layer extracted with ethyl acetate twice. The combined organic layers were washed with water and saturated brine, dried over Na₂SO₄, and concentrated *in vacuo*. The resulting residue was purified using silica gel column chromatography (hexane/ethyl acetate = 2/1) to give compound 33.2 as a white solid (0.93 mmol).



33.2

33.3

[00252] 2-{1-[4-(3-Methoxy-benzyloxy)-phenyl]-3-methyl-but-2-enyl}-malonic acid (33.3). To a solution of compound 33.2 (0.50g, 1.21 mmol) in THF (5 ml), methanol (5 ml) and water (2.5 ml) was added lithium hydroxide monohydrate (1.17g, 28 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was acidified with 1N HCl to pH 2-3, and then extracted with ethyl acetate twice. The organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The resulting residue was used for the next reaction without purification.



33.3

33

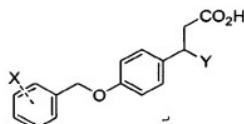
[00253] 3-[4-(3-Methoxy-benzyloxy)-phenyl]-5-methyl-hex-4-enoic acid (33). A suspension of compound 33.3 (0.136 mmol) in toluene was refluxed for 16h. After

removing the solvent, the residue was purified using silica gel column chromatography (TFA/ Dichloromethane/ ethyl acetate = 1/5/40) to give compound 33 as a white solid (0.088 mmol). MS ESI m/e: 339 (M-H). ^1H NMR (500MHz) (DMSO-d₆) δ 11.97 (1H, s); 7.31 (1H, t, J=10 Hz); 7.14 (2H, d, J=11 Hz); 6.99 (2H, m); 6.87 (3H, m); 5.22 (1H, m); 5.03 (2H, s); 3.75 (1H, m); 3.75 (3H, s); 2.44-2.53 (2H, m); 1.63 (3H, s); 1.62 (3H, s).

6.34 Example 34

[00254] The following compounds were made using the method described in Example 33.

TABLE 10



Compound	X	Y
34.1	4-Methoxy	1-Propenyl
34.2	4-Methoxy	3-Propenyl
34.3	4-Methoxy	Vinyl
34.4	4-Methoxy	2-Propenyl
34.5	4-Methoxy	2-Methyl-1-propenyl
34.6	4-Methoxy	1-Methyl-1-propenyl
34.7	4-Methoxy	Thiophen-2-yl
34.9	2-Methoxy	2-Methyl-1-propenyl
34.10	3-Methoxy	1-Propynyl
34.11	3-Ethoxy	2-Methyl-1-propenyl

[00255] Compound 34.1. MS ESI m/e: 325 (M-H). ^1H NMR (500MHz) (DMSO-d₆) δ 12.05 (1H, s); 7.36 (2H, d, J=10 Hz); 7.16 (2H, d, J=10 Hz); 6.94 (2H, d, J=10 Hz); 6.90 (2H, d, J=5 Hz); 5.48-5.58 (1H, m); 5.39-5.43 (1H, m); 4.98 (2H, s); 3.99-4.03 (1H, m); 3.76 (3H, s); 2.46-2.60 (2H, m); 1.64 (3H, d, J=5 Hz).

[00256] Compound 34.2. MS ESI m/e: 325 (M-H). ^1H NMR (500MHz) (DMSO-d₆) δ 11.98 (1H, s); 7.38 (2H, d, J=10 Hz); 7.13 (2H, m); 6.95 (2H, m); 6.09 (2H, m); 5.63 (1H, m); 4.97 (2H, s); 4.92 (2H, d, J=10 Hz); 3.76 (3H, s); 3.03 (1H, m); 2.28-2.56 (4H, m).

- [00257] Compound 34.3 MS ESI m/e: 311 (M-H). ^1H NMR (500MHz) (DMSO-d₆) δ 12.06 (1H, s); 7.37 (2H, d, J=10 Hz); 7.14 (2H, d, J=10 Hz); 6.92-6.95 (4H, m); 5.92 (1H, m); 5.00 (2H, m); 4.98 (2H, s); 3.76 (3H, s); 3.35 (1H, m); 2.54-2.64 (2H, m).

[00258] Compound 34.4 MS ESI m/e: 325 (M-H). ^1H NMR (500MHz) (DMSO-d₆) δ 12.03 (1H, s); 7.37 (2H, d, J=10 Hz); 7.09-7.19 (4H, m); 6.91-6.99 (4H, m); 4.97 (2H, s); 3.76 (3H, s); 3.63 (1H, m); 2.57-2.71 (2H, m); 2.09 (3H, s).

[00259] Compound 34.5 MS ESI m/e: 339 (M-H). ^1H NMR (500MHz) (DMSO-d₆) δ 11.97 (1H, s); 7.36 (2H, d, J=10 Hz); 7.14 (2H, d, J=10 Hz); 6.94 (2H, d, J=10 Hz); 6.89 (2H, d, J=5 Hz); 5.24 (2H, d, J=10 Hz); 3.85-3.90 (1H, m); 3.76 (3H, s); 2.44-2.57 (2H, m); 1.68 (3H, s); 1.63 (3H, d, J=10 Hz).

[00260] Compound 34.6 MS ESI m/e: 339 (M-H). ^1H NMR (500MHz) (DMSO-d₆) δ 11.97 (1H, s); 7.37 (2H, d, J=8.5 Hz); 7.10 (2H, d, m); 6.90-6.95 (4H, m); 5.23 (1H, d, J=6.5 Hz); 4.97 (2H, s); 4.29 (1H, m); 3.76 (3H, s); 2.47-2.75 (2H, m); 1.71 (3H, d, J=6 Hz); 1.56 (3H, s).

[00261] Compound 34.7 MS ESI m/e: 367 (M-H). ^1H NMR (500MHz) (DMSO-d₆) δ 12.18 (1H, s); 7.37 (2H, d, J=5 Hz); 7.32 (1H, m); 7.21 (2H, d, J=10 Hz); 6.92-6.95 (6H, m); 4.98 (2H, s); 4.58 (1H, m); 3.76 (3H, s); 3.01 (1H, m); 2.94 (1H, m).

[00262] Compound 34.9 MS ESI m/e: 339 (M-H). ^1H NMR (500MHz) (DMSO-d₆) δ 11.99 (1H, s); 7.37 (2H, m); 7.14 (2H, d, J=10 Hz); 7.04 (2H, d, J=10 Hz); 6.96 (1H, t, J=10 Hz); 6.88 (2H, d, J=10 Hz); 5.24 (2H, d, J=10 Hz); 5.00 (2H, s); 3.87 (1H, m); 3.87(3H, s); 2.45-2.55 (2H, m); 1.63 (3H, s).

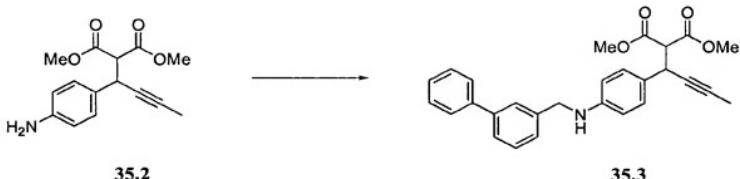
[00263] Compound 34.10 MS ESI m/e: 323 (M-H). ^1H NMR (500MHz) (DMSO-d₆) δ 12.10 (1H, s); 7.25-7.32 (3H, m); 7.01 (2H, d, J=9 Hz); 6.94 (2H, d, J=10 Hz); 6.88 (1H, m); 5.05 (2H, s); 3.92-3.95 (1H, m); 3.75 (3H, s); 2.58 (2H, d, J=10 Hz); 1.77 (3H, s).

6.35 Example 35

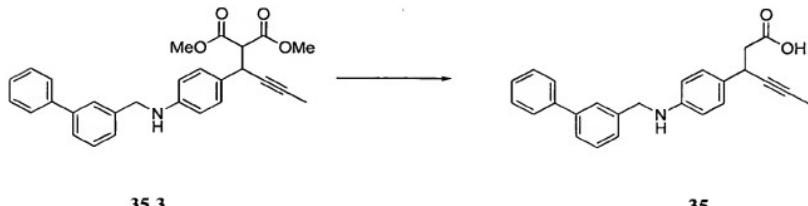
- [00264] The following example illustrates the preparation 3-[4-(3-Methoxy-benzyloxy)-phenyl]-5-methyl-hex-4-enoic acid.



[00265] 2-[1-(4-Amino-phenyl)-but-2-ynyl]-malonic acid dimethyl ester (35.2). Tin chloride dihydrate (46 mmol) was added to solution of compound 35.1 (15.3 mmol, prepared from commercially available dimethyl-4-nitrobenzylidinemalonate and 1-propynylmagnesium bromide according to the method in Example 33) in ethanol (200 ml). The mixture was stirred at 70 °C for 17 h. After removing solvent under reduced pressure, aqueous sodium carbonate solution was added and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, concentrated *in vacuo*. The resulting residue was filtered through short plug of silica gel, eluting with ethyl acetate. The eluant was concentrated to obtain compound 35.2 (12.8 mmol).



[00266] 2-(1-{4-[(Biphenyl-3-ylmethyl)-amino]-phenyl}-but-2-ynyl)-malonic acid dimethyl ester (35.3). A mixture of compound 35.2 (1.0 mmol), 3-(bromomethyl)biphenyl (1.3 mmol) and K₂CO₃ (2.0 mmol) in DMF (10ml) was stirred at 90 °C for 19 h. After diluting with ethyl acetate, the mixture was washed with aqueous Na₂CO₃ and then with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The resulting residue was purified using silica gel column chromatography (hexane/ethyl acetate = 2/1) to give compound 35.3.



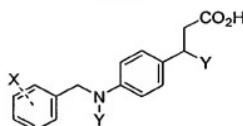
[00267] 3-{4-[(Biphenyl-3-ylmethyl)-amino]-phenyl-hex-4-ynoic acid (35). Compound 35 was prepared from compound 35.3 by hydrolysis with base and decarboxylation as described in Example 33. MS ESI m/e: 368 (M-H). ^1H NMR (500MHz) ($\text{DMSO}-d_6$) δ 7.63-7.66 (2H, m); 7.51(1H, m); 7.34-7.44 (6H, m); 7.05 (2H, d, $J=10$ Hz);

6.60 (2H, d, $J=10$ Hz); 4.33 (2H, s); 3.79-3.83 (1H, m); 2.44-2.53 (2H, m); 2.09 (1H, s); 1.74 (3H, s).

6.36 Example 36

[00268] The following compounds were prepared according to the methods described in Example 35.

TABLE 11



Compound	X	Y	Z
36.1	3-Methoxy	H	1-Propynyl
36.2	3-Methoxy	3-Methoxy-benzyl	1-Propynyl
36.3	4-Phenyl	H	1-Propynyl
36.4	4-(2-cyanophenyl)	H	1-Propynyl

6.37 Example 37

[00269] This example illustrates the preparation of (+/-)-3-(4-[(4-methoxyphenyl)methoxy]- phenyl)-propanoic acid.



[00270] (+/-)-3-(4-[(4-methoxyphenyl)methoxy]phenyl)-propanoic acid (37). To a stirring ethyl acetate (100mL) solution of 5-[[4-[(4-methoxyphenyl)methoxy]phenyl]-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (200mg, 0.543mmol) was added EtOH (4mL), followed by NaBH4 (62mg, 1.63mmol). The reaction mixture was stirred at room temperature for 15 minutes, quenched with water (5mL), extracted with EtOAc (10mL). The extract was washed with brine, dried over MgSO4, filtered, and concentrated to a white solid. A solution of this white solid in 3:1 pyridine-water (5mL) was heated at 100 °C for

24h. The reaction mixture was cooled to room temperature and put in an ice-water bath. Concentrated HCl was carefully added to pH ~2. The resulting suspension was extracted with ethyl acetate (10mL x 3), dried over MgSO₄, filtered, and concentrated to an off-white solid. Preparative HPLC gave compound 37 as a white solid. MS ESI (neg.) m/e: 285.0 (M - 1).

6.38 Example 38

[00271] This example illustrates the preparation of (+/-)-3-(4-[(4-methoxyphenyl)methoxy]- phenyl)-3-cyano-propanoic acid.

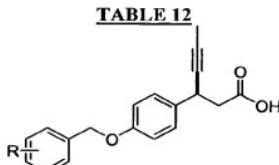


[00272] (+/-)-3-(4-[(4-methoxyphenyl)methoxy]phenyl)-3-cyano-propanoic acid (38). To a stirred DMF (10mL) solution of 2-[4-[(4-Methoxyphenyl)methoxy]phenyl]-acetonitrile (500mg, 1.97mmol) was added ethyl bromoacetate (330 μ L, 2.96mmol), followed by K₂CO₃ (820mg, 5.9mmol). The reaction mixture was stirred at room temperature for 2h, poured into ice water (100mL), filtered, and dried to a white solid. 20mg of this white solid in 1:1 THF/1N NaOH in MeOH (4mL) was stirred for 5h. The reaction mixture was concentrated, diluted with water (10mL), washed with EtOAc (5mL x 2). The aqueous layer was acidified with 3N HCl to pH ~2, extracted with EtOAc (10mL x 2), dried over MgSO₄, filtered, and concentrated to a white solid. MS ESI (neg.) m/e: 310.0 (M - 1).

6.39 Example 39

[00273] The following compounds were prepared by the methods described in Example 15 using the enantiomer with the shorter retention time from the chiral HPLC resolution.

TABLE 12



Compounds	R	Compounds	R
15	2-CH ₃	39.4	4-(2-CN)Ph
39.1	3-CH ₃	39.5	3-CF ₃
39.2	3-CF ₃ O	39.6	4-Br
39.3	3-Cl	39.7	4-CH ₃ O

[00274] (3*S*)-3-[4-(3-Methyl-benzyloxy)-phenyl]-hex-4-yneic acid (39.1). MS-ESI (neg.) m/e: 307.1 (M-H). $[\alpha]^{20}$: +21.26 (c0.188, DMF).

[00275] (3*S*)-3-[4-(3-Trifluoromethoxy-benzyloxy)-phenyl]-hex-4-yneic acid (39.2). MS-ESI (neg.) m/e: 377.0 (M-H). $[\alpha]^{20}$: +18.30 (c0.259, DMF).

[00276] (3*S*)-3-[4-(3-chlorobenzyloxy)-phenyl]-hex-4-yneic acid (39.3). MS-ESI (neg.) m/e: 327.1 (M-H). $[\alpha]^{20}$: +14.36 (c0.440, DMF).

[00277] (3*S*)-3-[4-(2'-Cyano-biphenyl-4-ylmethoxy)-phenyl]-hex-4-yneic acid (39.4). MS-ESI (neg.) m/e: 394.1 (M-H). $[\alpha]^{20}$: +16.07 (c0.331, DMF).

[00278] (3*S*)-3-[4-(2-Tirfluoromethyl-benzyloxy)-phenyl]-hex-4-yneic acid (39.5). MS-ESI (neg.) m/e: 361.1 (M-H). $[\alpha]^{20}$: +12.80 (c0.285, DMF).

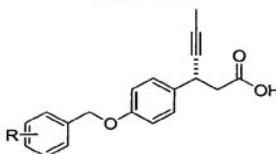
[00279] (3*S*)-3-[4-(4-Bromobenzyloxy)-phenyl]-hex-4-yneic acid (39.6). MS-ESI (neg.) m/e: 371.0, 373.0 (M-H). $[\alpha]^{20}$: +19.19 (c0.238, DMF).

[00280] (3*S*)-3-[4-(4-Methoxy-benzyloxy)-phenyl]-hex-4-yneic acid (39.7). MS-ESI (neg.) m/e: 323.0 (M-H). $[\alpha]^{20}$: +23.30 (c0.329, DMF).

6.40 Example 40

[00281] The following compounds were prepared by the methods described in Example 15 using the enantiomer with longer retention time from the chiral HPLC resolution.

TABLE 13



Compounds	R	Compounds	R
40.1	2-CH ₃	40.4	3-CF ₃
40.2	3-Cl	40.5	4-CH ₃ O

[00282] **(3*R*)-3-[4-(2-Methyl-benzylxy)-phenyl]-hex-4-yneic acid (40.1).** ¹H NMR (400 MHz, acetone-d₆) δ 7.45 (d, 1H, J=7.11 Hz); 7.37 (d, 2H, J=8.58 Hz); 7.26 (d, 1H, J=1.62 Hz); 7.22-7.27 (m, 2H); 7.00 (d, 2H, J=8.76 Hz); 5.11 (s, 2H); 4.05 (m, 1H); 3.33 (s, 1H); 2.69 (m, 2H); 2.38 (s, 3H); 1.80 (d, 3H, J=2.44). MS-ESI (neg.) m/e: 307.1 (M-H). [α]²⁰: -19.78 (c0.286, DMF).

[00283] **(3*R*)-3-[4-(3-chlorobenzylxy)-phenyl]-hex-4-yneic acid (40.2).** MS-ESI (neg.) m/e: 327.0 (M-H). [α]²⁰: -20.50 (c0.158, DMF).

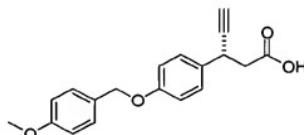
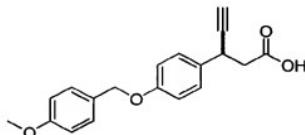
[00284] **(3*R*)-3-[4-(2'-Cyano-biphenyl-4-ylmethoxy)-phenyl]-hex-4-yneic acid (40.3).** MS-ESI (neg.) m/e: 394.1 (M-H). [α]²⁰: -25.04 (c0.143, DMF).

[00285] **(3*R*)-3-[4-(2-Tirfluoromethyl-benzylxy)-phenyl]-hex-4-yneic acid (40.4).** MS-ESI (neg.) m/e: 361.0 (M-H). [α]²⁰: -14.69 (c0.286, DMF).

[00286] **(3*R*)-3-[4-(4-Methoxy-benzylxy)-phenyl]-hex-4-yneic acid (40.9).** MS-ESI (neg.) m/e: 323.0 (M-H). [α]²⁰: -27.20 (c0.324, DMF).

6.41 Example 41

[00287] The following compounds were prepared by the methods similar to those of example 15.



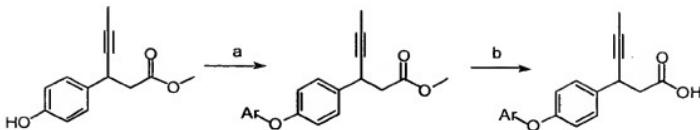
[00288] **(3*S*)-3-[4-(4-Methoxy-benzylxy)-phenyl]-pent-4-yneic acid (41.1).** MS-ESI (pos.) m/e: 333.1 (M+H). [α]²⁰: +11.80 (c0.166, DMF).

[00289] **(3*R*)-3-[4-(4-Methoxy-benzylxy)-phenyl]-pent-4-yneic acid (41.2).** MS-ESI (pos.) m/e: 333.1 (M+H). [α]²⁰: -10.20 (c0.206, DMF).

6.42 Example 42

[00290] Scheme 42.1 presents a general procedure for preparation of diaryl ether compounds.

Scheme 42.1



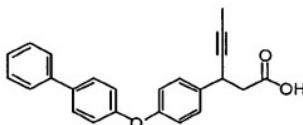
Scheme X. a. ArB(OH)₂, CuO(Ac)₂, Et₃N, DCM, 4A MS, r.t., 16h; b. LiOH/THF, MeOH, and water, r.t., 2h.

42.1

42.2

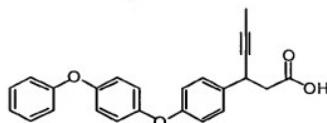
42.3

[00291] General procedure for preparation of diaryl ether compounds: A flask is charged with phenol (1.0 equiv.), Cu(OAc)₂ (1.0 equiv.), arylboronic acid (1.0-3.0 equiv.), powdered 4 Å molecular sieves. The reaction mixture was diluted with CH₂Cl₂ to yield a solution approximately 0.1 M in phenol, and Et₃N (5.0 equiv.) is added. After stirring the heterogeneous reaction mixture for 16h at 25 °C under ambient atmosphere, the resulting slurry is filtered and the diaryl ether is isolated from the organic filtrate by flash chromatography. The resulted ester was then hydrolyzed with LiOH (2.0 equiv.) in a 1:1:1 mixture of MeOH, THF, and water for 2h at 25 °C. The reaction mixture was acidified with 1N HCl, extracted with CH₂Cl₂ and concentrated to give the pure acid.



42.4

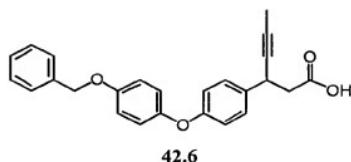
[00292] 3-[4-(Biphenyl-4-yloxy)-phenyl]-hex-4-ynoic acid (42.4). MS ESI m/e: 357.0 (M + H). ¹H NMR (500 MHz) (CDCl₃) δ 7.60-7.57 (4H, m); 7.46 (2H, dd, *J*=8.0, 8.0 Hz); 7.39 (2H, d, *J*=8.5 Hz); 7.36 (1H, d, *J*=7.3 Hz); 7.09 (2H, d, *J*=8.6 Hz); 7.04 (2H, d, *J*=8.6 Hz); 4.2-4.1 (1H, m); 2.87 (1H, dd, *J*=15.8, 8.6 Hz); 2.77 (1H, dd, *J*=15.8, 6.7 Hz); 1.88 (3H, d, *J*=2.3 Hz).



42.5

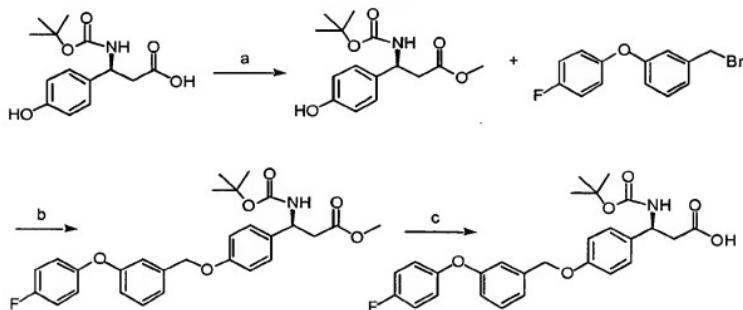
[00293] 3-[4-(4-Phenoxy-phenoxy)-phenyl]-hex-4-ynoic acid (42.5). MS ESI m/e: 373.0 (M + H). ¹H NMR (500 MHz) (CDCl₃) δ 7.37-7.32 (5H, m); 7.12 (2H, dd, *J*=8.0, 8.0 Hz)

Hz); 7.03 (2H, d, $J=7.5$ Hz); 7.02 (2H, s); 6.97 (2H, d, $J=8.6$ Hz); 4.1 (1H, m); 2.85 (1H, dd, $J=15.8, 8.6$ Hz); 2.75 (1H, dd, $J=15.8, 6.7$ Hz); 1.87 (3H, d, $J=2.3$ Hz).



[00294] **3-[4-(4-Benzylxy-phenoxy)-phenyl]-hex-4-yneoic acid (42.6).** MS ESI m/e: 387.0 (M + H). ^1H NMR (500 MHz) (CDCl_3) δ 7.47 (2H, d, $J=7.2$ Hz); 7.42 (2H, dd, $J=7.5, 7.5$ Hz); 7.37 (1H, d, $J=7.3$ Hz); 7.33 (2H, d, $J=8.7$ Hz); 6.98 (4H, br. s); 6.93 (2H, d, $J=9.7$ Hz); 5.07 (2H, s); 4.10 (1H, m); 2.84 (1H, dd, $J=15.7, 8.5$ Hz); 2.75 (1H, dd, $J=15.7, 6.7$ Hz); 1.86 (3H, d, $J=2.3$ Hz).

Scheme 42.2

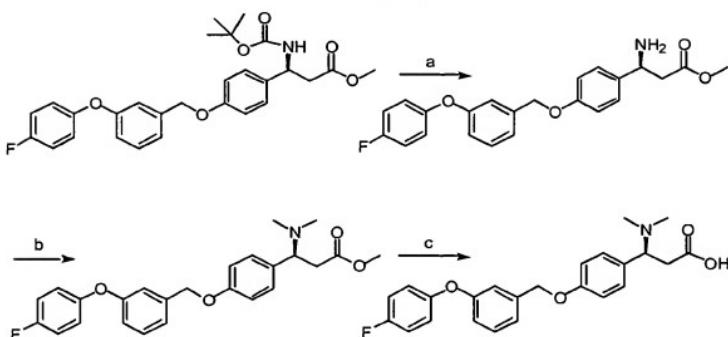


Scheme X. a. TMSCHN₂, MeOH, benzene, r.t., 1h; b. K₂CO₃, DMF, r.t., overnight; c. LiOH/THF, MeOH, and water, r.t., 2h.

[00295] **(S)-3-tert-Butoxycarbonylamino-3-[4-(3-(4-fluoro-phenoxy)-benzyloxy)-phenyl]-propionic acid (x.x).** 3-Boc-amino-3-(4-hydroxyphenyl)-propanoic acid (703 mg, 2.5 mmol) in 25mL of MeOH/Benzene (4:1) was slowly added 2.5 mL of 2M solution of trimethylsilyldiazomethane in hexane at 25 °C. The reaction mixture was stirred for 1h and concentrated in vacuo to give the methyl ester. MS ESI m/e: 296.0 (M + H). To a solution of the methyl ester (2.5 mmol) and 4-fluorophenoxybenzyl bromide (700mg, 2.5 mmol) in DMF (10 mL), was added K₂CO₃ (414mg, 3 mmol) and the resulting mixture was stirred

overnight (14~16h) at 25 °C. The solution was diluted with water (20mL) and extracted with EtOAc twice (20 mL). The organic extraction was concentrated and the product was purified by flash chromatography. MS ESI m/e: 518.0 (M + Na). The methyl ester (39mg, 0.08 mmol) was hydrolyzed with LiOH (10mg, 0.25 mmol) in a 1.5 mL of 1:1:1 mixture of MeOH, THF, and water for 2h at 25 °C. The reaction mixture was acidified with 1N HCl, extracted with CH₂Cl₂ and concentrated to give the pure acid. MS ESI m/e: 504.0 (M + Na). ¹H NMR (400MHz) (CDCl₃) δ 8.5 (1H, br. s); 7.34 (1H, dd, *J*=8.0, 8.0 Hz); 7.24 (2H, d, *J*=8.8 Hz); 7.16 (1H, d, *J*=7.7 Hz); 7.07-6.98 (5H, m); 6.93 (2H, d, *J*=11.7 Hz); 6.92 (1H, d); 5.3 (1H, br. s); 5.03 (2H, s); 3.0-2.8 (2H, m); 2.1-1.9 (1H, m); 1.44 (9H, s).

Scheme 42.3



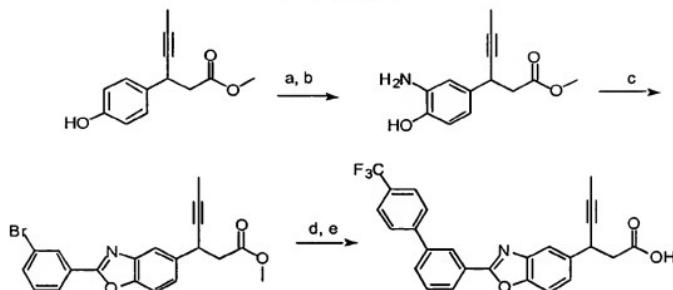
Scheme X. a. TFA, DCM, r.t., 1h; b. formaldehyde, NaBH(OAc)₃, AcOH, DMF, r.t., overnight; c. LiOH/THF, MeOH, and water, r.t., 2h.

[00296] **3-Dimethylamino-3-[4-[3-(4-fluoro-phenoxy)-benzyloxy]-phenyl]-propionic acid (x.x).** (*S*)-3-*tert*-Butoxycarbonylamino-3-[4-[3-(4-fluoro-phenoxy)-benzyloxy]-phenyl]-propionic acid methyl ester (1.0 g, 2 mmol) was treated with 10 mL of 10% TFA solution in CH₂Cl₂ at 25 °C for 1h. The solvent was concentrated in vacuo to give the free amine. MS ESI m/e: 418.0 (M + Na). The amine (60 mg, 0.15 mmol) was treated with excess formaldehyde (2 equiv.), NaBH(OAc)₃ (85 mg, 0.4 mmol) and catalytic amount of AcOH in DMF overnight (14~16h) at 25 °C. The product was purified by reverse phase HPLC. MS ESI m/e: 424.1 (M + H). The methyl ester was hydrolyzed with LiOH (19mg, 0.45 mmol) in a 3 mL of 1:1:1 mixture of MeOH, THF, and water for 2h at 25 °C. The reaction mixture was acidified with 1N HCl, extracted with CH₂Cl₂ and concentrated to give the pure acid (23 mg). MS ESI m/e: 410.2 (M + H). ¹H NMR (500MHz) (CDCl₃) δ 9.46 (1H, br. s); 7.72 (1H, d, *J*=16.0 Hz); 7.51 (2H, d, *J*=8.7 Hz); 7.36 (1H, dd, *J*=8.0, 8.0 Hz);

Hz); 7.17 (2H, d, *J*=7.0 Hz); 7.08-6.98 (5H, m); 6.94 (1H, d, *J*=8.2 Hz); 6.34 (1H, d, *J*=16.0 Hz); 5.10 (2H, s); 3.4-2.9 (2H, m); 2.73 (6H, s); 2.1-1.9 (1H, m).

6.43 Example 43

Scheme 43.1

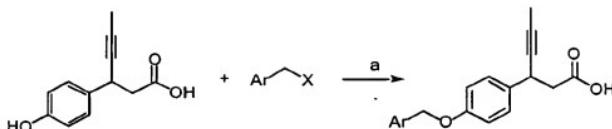


Scheme X. a. HNO_3 , HOAc , 80°C , 3h; b. SnCl_2 , EtOAc/EtOH , 70°C , 3h; c. 3-bromobenzaldehyde, DDQ, DMF, r.t., 2h; d. 4-trifluoromethylbezeneboronic acid, $\text{Pd}(\text{PPh}_3)_4$, DME, Na_2CO_3 , 80°C , 14h; e. LiOH/THF , MeOH , and water, r.t., 2h.

[00297] **3-[2-(4'-Trifluoromethyl-biphenyl-3-yl)-benzoxazol-5-yl]-hex-4-ynoic acid.** 3-(4-Hydroxy-phenyl)-hex-4-ynoic acid methyl ester (1.32 g, 6 mmol) was treated with HNO_3 (0.30 mL, 7.2 mmol) in AcOH (10 mL) at 80°C for 3h. The solvent was concentrated in vacuo and 3-(3-nitro-4-hydroxy-phenyl)-hex-4-ynoic acid methyl ester (613 mg, 2.3 mmol) was isolated from flash chromatography. MS ESI m/e: 264.0 ($M + H$). The nitro group was then reduced with SnCl_2 (2.62 g, 11.6 mmol) in EtOH (10 mL) and EtOAc (10 mL) at 70°C for 3h. The reaction mixture was cooled to 25°C , washed with saturated aqueous Na_2CO_3 , water, brine, dried over MgSO_4 , filtered and concentrated in vacuo. The crude product was then purified by reverse phase HPLC to give 3-(3-amino-4-hydroxy-phenyl)-hex-4-ynoic acid methyl ester (174 mg, 0.74 mmol). MS ESI m/e: 234.0 ($M + H$). 3-(3-amino-4-hydroxy-phenyl)-hex-4-ynoic acid methyl ester (174 mg, 0.74 mmol) and 3-bromobenzaldehyde (278 mg, 1.5 mmol) in DMF (3 mL) was treated with DDQ (204 mg, 0.9 mmol) for 2h at 25°C . The product was purified by reverse phase HPLC. MS ESI m/e: 398.0 ($M + H$). 3-[2-(3-Bromo-phenyl)-benzoxazol-5-yl]-hex-4-ynoic acid methyl ester (19.6 mg, 0.05 mmol) and trifluorophenylboronic acid (38 mg, 0.2 mmol) in DME (1 mL) and 0.2 mL of 2M solution of aqueous Na_2CO_3 was treated with $\text{Pd}(\text{PPh}_3)_4$ at 80°C for 14h. The product was isolated from flash chromatography. MS ESI m/e: 464.0 ($M + H$). The methyl ester (7.8 mg, 0.017 mmol) was hydrolyzed with LiOH (4mg, 0.1 mmol) in a 1

mL of 1:1:1 mixture of MeOH, THF, and water for 2h at 25 °C. The reaction mixture was acidified with 1N HCl, extracted with CH₂Cl₂ and concentrated to give the pure acid (7.6 mg). MS ESI m/e: 450.1 (M + H). ¹H NMR (500 MHz) (CDCl₃) δ 8.52 (1H, s); 8.30 (1H, d, *J*=7.8 Hz); 7.91 (1H, s); 7.83 (2H, d, *J*=8.2 Hz); 7.82 (1H, s); 7.78 (2H, dd, *J*=8.0, 8.0 Hz); 7.67 (1H, dd, *J*=7.8, 7.8 Hz); 7.58 (2H, d, *J*=8.4 Hz); 7.46 (1H, dd, *J*=8.4, 1.5 Hz); 4.29 (1H, m); 2.94 (1H, dd, *J*=15.8, 8.1 Hz); 2.84 (1H, dd, *J*=15.8, 6.9 Hz); 1.89 (3H, d, *J*=2.3 Hz).

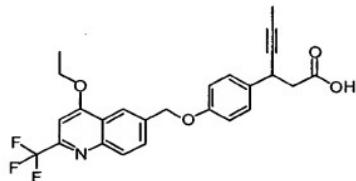
6.44 Example 44



Scheme X. a. NaOH, EtOH, water, r.t., 3h (X = Br, Cl).

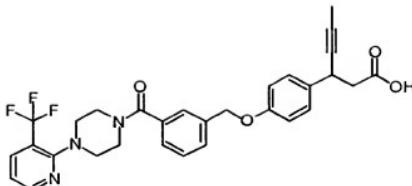
Scheme 44.1

[00298] General procedure for the preparation of aryl benzyl ethers: 3-(4-Hydroxy-phenyl)-hex-4-ynoic acid in EtOH (0.4M) was added IN NaOH solution (3 equiv.) in water at 25 °C and stirred fro 5 minutes at 70 °C. ArCH₂X (X = Br, Cl, 1 equiv.) in EtOH (0.2M) was slowly added, stirred for 3h at 70 °C. The reaction mixture was acidified with 1N HCl and purified from reverse phase HPLC.



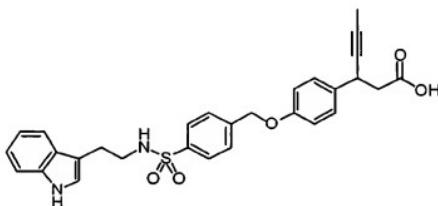
44.3

[00299] 3-[4-(4-Ethoxy-2-trifluoromethyl-quinolin-6-ylmethoxy)-phenyl]-hex-4-ynoic acid (44.3). MS ESI m/e: 458.0 (M + H). ¹H NMR (400 MHz) (DMSO-*d*₆) δ 12.6 (1H, br. s); 8.31 (1H, s); 8.12 (1H, d, *J*=8.7 Hz); 7.95 (1H, dd, *J*=8.7, 1.3 Hz); 7.41 (1H, s); 7.31 (2H, d, *J*=8.5 Hz); 7.03 (2H, d, *J*=8.5 Hz); 5.36 (2H, s); 4.47 (2H, q, *J*=8.0 Hz); 3.96 (1H, m); 2.62 (2H, d, *J*=7.6 Hz); 1.79 (3H, d, *J*=1.9 Hz); 1.21 (3H, t, *J*=8.0 Hz).



44.4

[00300] **3-(4-[3-(4-(3-Trifluoromethyl-pyridin-2-yl)-piperazine-1-carbonyl]-benzyloxy)-phenyl-hex-4-ynoic acid.** MS ESI m/e: 552.0 (M + H). ^1H NMR (400 MHz) (DMSO- d_6) δ 12.5 (1H, br. s); 8.57 (1H, d, J =3.5 Hz); 8.12 (1H, dd, J =7.9, 1.6 Hz); 7.56-7.48 (3H, m); 7.41 (1H, d, J =7.5 Hz); 7.30-7.25 (3H, m); 6.98 (2H, d, J =8.7 Hz); 5.16 (2H, s); 3.95 (1H, m); 3.2 (4H, m); 2.60 (2H, d, J =7.6 Hz); 2.52 (4H, m); 1.77 (3H, d, J =2.4 Hz).



44.5

[00301] **3-(4-[4-[2-(1H-Indol-3-yl)-ethylsulfamoyl]-benzyloxy)-phenyl-hex-4-ynoic acid.** MS ESI m/e: 517.2 (M + H). ^1H NMR (400 MHz) (DMSO- d_6) δ 12.5 (1H, br. s); 10.82 (1H, s); 7.83 (2H, d, J =8.3 Hz); 7.77 (1H, dd, J =7.8, 7.8 Hz); 7.39 (1H, d, J =8.0 Hz); 7.32 (1H, d, J =8.0 Hz); 7.29 (2H, d, J =8.7 Hz); 7.13 (1H, d, J =2.2 Hz); 7.06 (1H, dd, J =7.0, 8.0 Hz); 6.97 (2H, d, J =8.7 Hz); 5.19 (2H, s); 3.95 (1H, m); 3.02 (2H, t, J =7.6 Hz); 2.81 (2H, t, J =7.6 Hz); 2.61 (2H, d, J =8.0 Hz); 1.78 (3H, d, J =2.4 Hz).

6.45 Example 45: Cell-based Aequorin Assay

[00302] A cell-based Aequorin assay may be employed to characterize the modulatory activity of compounds on the GPR40 signaling pathway. In a exemplary assay, CHO cells are transfected in a 15 cm plated containing 14 million cells with 5 μg of GPR40 expression vector and 5 μg of Aequorin expression vector (Euroscren) using Lipofectamine 2000 (Invitrogen). After 17-24 hours post-transfection, cells are washed

with phosphate buffered saline (PBS) and detached from the tissue culture dish with 2 mL of trypsin. Trypsinization is halted with 28 mL of Hanks Buffered Salt Solution containing 20 mM Hepes (H/HBSS) and 0.01% fatty acid-free bovine serum albumin (BSA) or 0.625% fatty acid-free human serum albumin (HSA). Coelantrazine is added to 1 ug/mL and the cells are incubated for 2 hours at room temperature. Cells are gently mixed every 15 minutes. Compounds are dissolved in dimethyl sulfoxide for preparation of 10 mM stock solutions. Compounds are diluted in H/HBSS containing either 0.01% BSA or 0.625% HSA. Serial dilutions of the test compounds are prepared to determine dose response.

[00303] Aequorin luminescence measurements are made using an EG&G Berthold 96-well luminometer and the response is measured over a 20 second interval after cells and compounds were mixed. The area-under-curve from 2-20 seconds is plotted to determine dose response. The EC₅₀ (effective concentration to reach 50% maximal response) is determined from the dose response plot.

[00304] **Table 14** presents representative data (EC₅₀ values) obtained for exemplary compounds of the invention comparing activation of human GPR40 to activation of mouse GPR40. **Table 15** presents the relative activation of human GPR40 by a number of exemplary compounds of the invention.

6.46 Example 46: Insulin Secretion Assay

[00305] C57/Bl6 mice are euthanized with carbon dioxide gas. The pancreatic bile duct is clamped proximal to the duodenum and then cannulated. H/HBSS containing 0.75 mg/ml collagenase XI (Sigma) is then infused into the pancreas through the cannula. The pancreas is excised and then incubated at 37°C for 13 minutes to complete enzymatic digestion. The collagenase digestion is quenched in H/HBSS containing 1% BSA and washed once in the same buffer. Islets can be purified using density gradient centrifugation using Histopaque (Sigma) and are hand-picked under a stereomicroscope.

[00306] Islets are cultured overnight in Roswell Park Memorial Institute (RPMI) media containing 10% fetal bovine serum and 50 uM beta-mercaptoethanol. Following overnight culture, islets are incubated in Dulbecco's Modification of Eagle's medium (DMEM) containing 2.8 mM glucose for one hour.

[00307] For determination of insulin secretion, islets are incubated in DMEM containing 12.5 mM glucose and test compounds for one hour. Insulin released into the culture medium from the islets is measured using an insulin ELISA.

[00308] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were

specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

TABLE 14

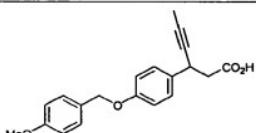
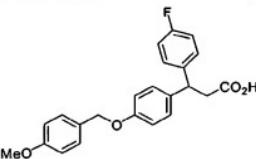
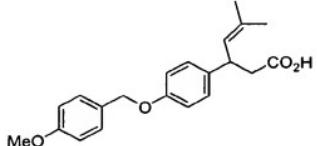
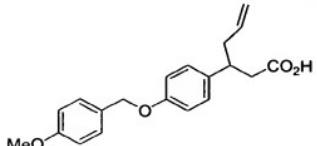
No.	Structure	Aequorin Assay*	
		Human GPR40 EC ₅₀	Mouse GPR40 EC ₅₀
12		+++	+++
14		+++	+++
34.5		+++	++
34.4		++	+

TABLE 14

No.	Structure	Aequorin Assay*	
		Human GPR40 EC ₅₀	Mouse GPR40 EC ₅₀
39.7		++++	+++
40.5		++	+
17.6		+++	+++
39		++++	++++
6.5		++++	++++

TABLE 14

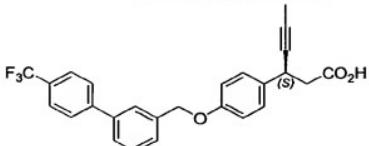
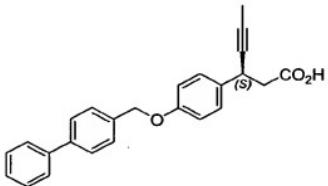
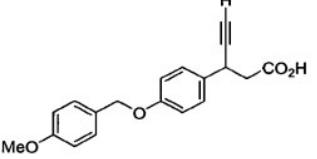
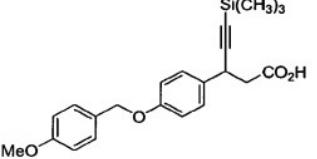
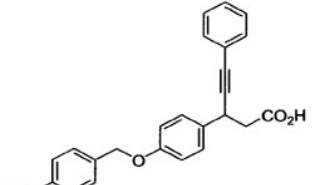
No.	Structure	Aequorin Assay*	
		Human GPR40 EC ₅₀	Mouse GPR40 EC ₅₀
2		++++	++++
7.3		++	++
34.10		+++	++
14.1		++	+
14.6		++	++

TABLE 14

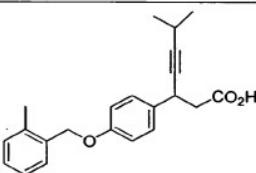
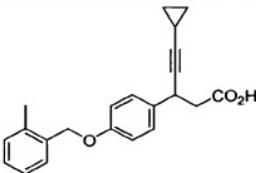
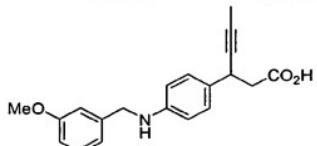
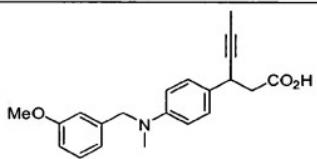
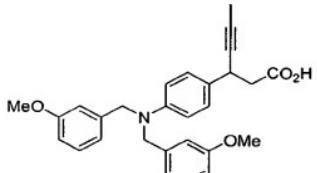
No.	Structure	Aequorin Assay*	
		Human GPR40 EC ₅₀	Mouse GPR40 EC ₅₀
		+++	+++
		+++	++++
36.1		+++	+++
		++	++
36.2		+++	+++

TABLE 14

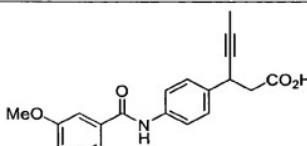
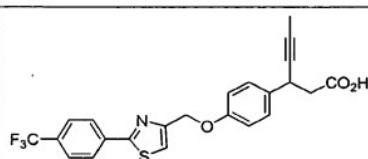
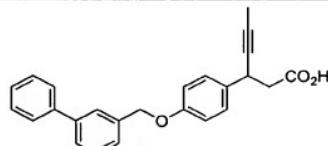
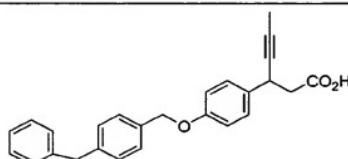
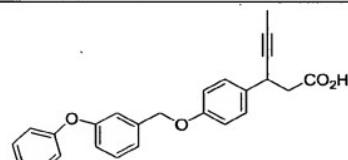
No.	Structure	Aequorin Assay*	
		Human GPR40 EC ₅₀	Mouse GPR40 EC ₅₀
		++	+++
		++++	++++
6.1		++++	+++
		++++	++++
		++++	++++

TABLE 14

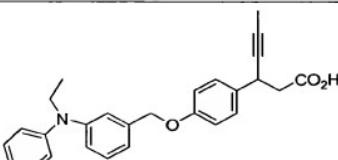
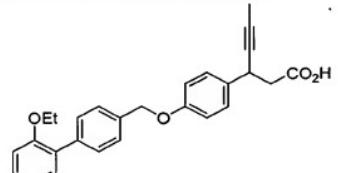
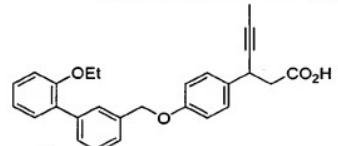
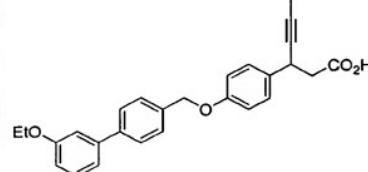
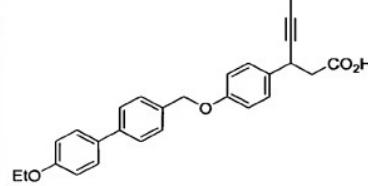
No.	Structure	Aequorin Assay*	
		Human GPR40 EC ₅₀	Mouse GPR40 EC ₅₀
		++++	++++
6.2		++++	+++
		++++	++++
		+++	+++
6.3		+++	+++

TABLE 14

No.	Structure	Aequorin Assay*	
		Human GPR40 EC ₅₀	Mouse GPR40 EC ₅₀
		++++	+++
		+++	+++
6.9		++++	++++
6.8		++++	+++
		++++	+++

TABLE 14

No.	Structure	Aequorin Assay*	
		Human GPR40 EC ₅₀	Mouse GPR40 EC ₅₀
6.7		++++	++++

* EC₅₀ Ranges:

- + EC₅₀ > 10 μM
- ++ 1 μM ≤ EC₅₀ ≤ 10 μM
- +++ 0.1 μM ≤ EC₅₀ < 1 μM
- ++++ 0.01 μM ≤ EC₅₀ < 0.1 μM
- +++++ EC₅₀ < 0.01 μM

TABLE II
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC ₅₀
		++
		++
		+
17.8		++
28		+++
		+++

TABLE II
Aequorin Assay Using Human GPR40

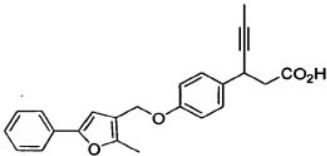
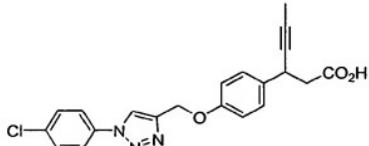
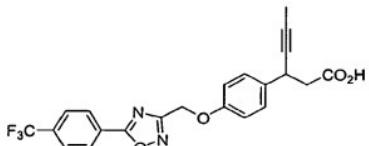
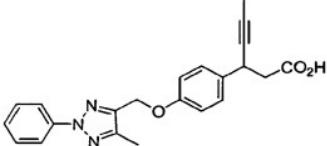
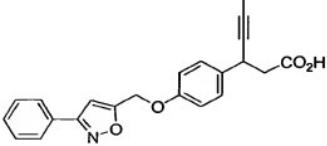
No.	Structure	Relative EC ₅₀
		++++
		++
26.1		+++
		++++
		+++

TABLE II
Aequorin Assay Using Human GPR40

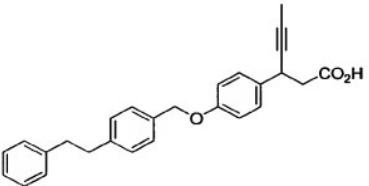
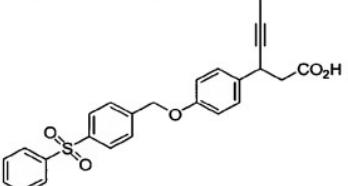
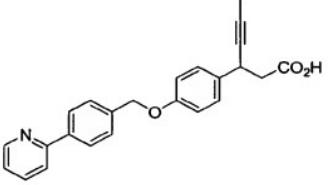
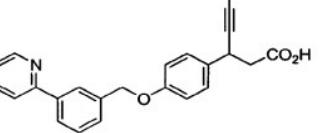
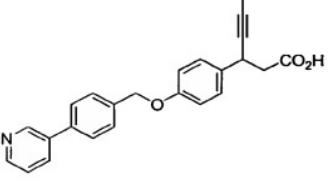
No.	Structure	Relative EC ₅₀
		+++
		+++
49		++++
50		+++
51		++

TABLE II
Aequorin Assay Using Human GPR40

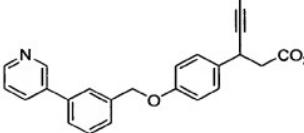
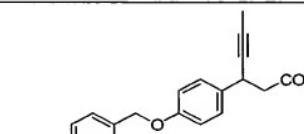
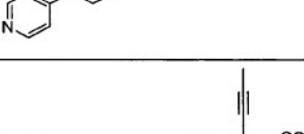
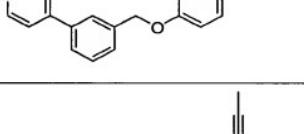
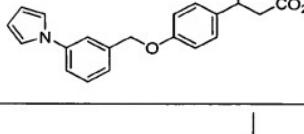
No.	Structure	Relative EC ₅₀
52		+++
53		+++
54		+++
55		++++
56		++

TABLE II
Aequorin Assay Using Human GPR40

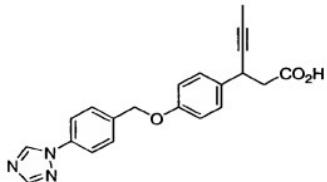
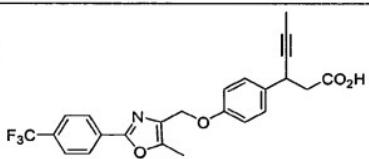
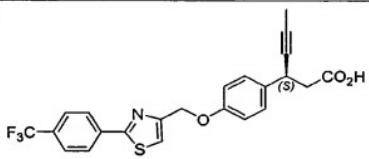
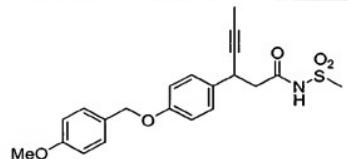
No.	Structure	Relative EC ₅₀
57		++
58		++++
59		+++++
60		++
61		++

TABLE II
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC ₅₀
62		+++
63		++
64		++++
65		++++
66		++++

TABLE II
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC ₅₀
67		+++
68		++++
69		++++
70		+++++
71		+++++
72		+++

TABLE II
Aequorin Assay Using Human GPR40

No.	Structure	Relative EC ₅₀
73		+++
74		++
75		++++
76		++
77		+++
78		+++

TABLE II
Aequorin Assay Using Human GPR40

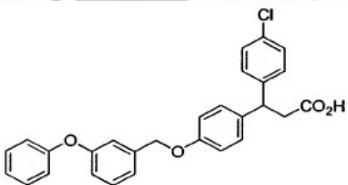
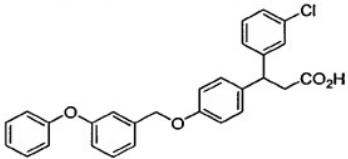
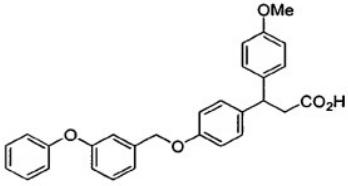
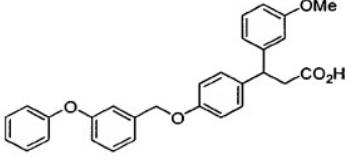
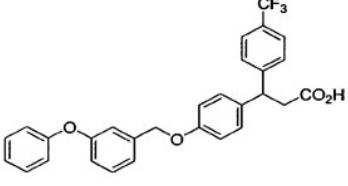
No.	Structure	Relative EC ₅₀
79		+++
80		+++
		+++
		+++
		++

TABLE II
Aequorin Assay Using Human GPR40

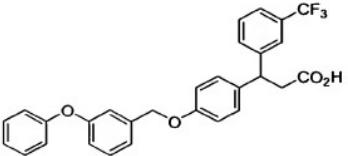
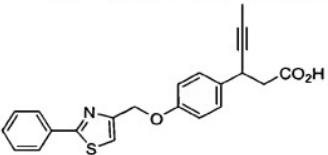
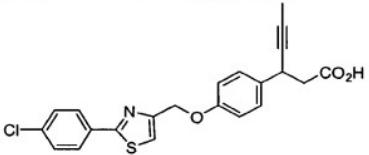
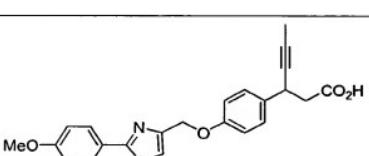
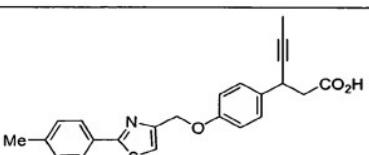
No.	Structure	Relative EC ₅₀
		+++
8.2		++++
8.3		++++
8.4		++++
8.5		++++

TABLE II
Aequorin Assay Using Human GPR40

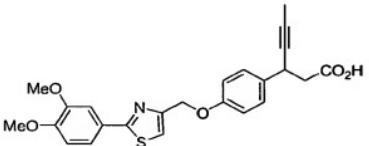
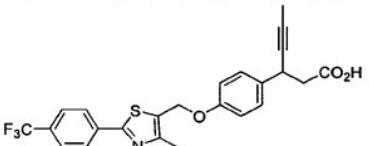
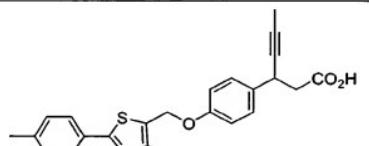
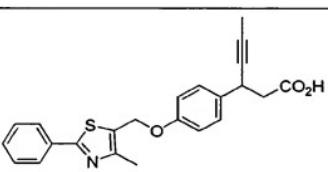
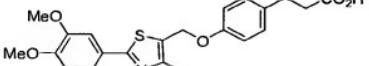
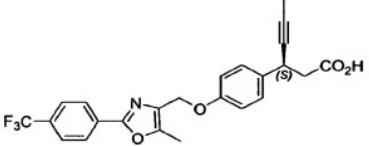
No.	Structure	Relative EC ₅₀
8.6		+++
9.1		++++
9.2		+++++
9.3		++++
9.4		++++
		+++++

TABLE II
Aequorin Assay Using Human GPR40

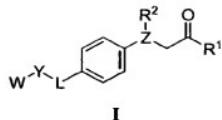
No.	Structure	Relative EC ₅₀
3		+++++

* EC₅₀ Ranges:

- + EC₅₀ > 10 μM
- ++ 1 μM ≤ EC₅₀ ≤ 10 μM
- +++ 0.1 μM ≤ EC₅₀ < 1 μM
- ++++ 0.01 μM ≤ EC₅₀ < 0.1 μM
- +++++ EC₅₀ < 0.01 μM

WHAT IS CLAIMED:

1. A compound having the formula (I):



or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein

R¹ is -H, -OH, -NHS(O₂)CH₃, heteroaryl, or -NH-heteroaryl;

R² is -(C₂-C₈)alkyl, -(C₃-C₈)alkenyl, -NR³R⁴, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, —C≡N, or —C≡C-R⁵;

R³ and R⁴ are independently -H, -(C₁-C₅)alkyl, or -(C₁-C₅)oxyalkyl;

R⁵ is -H, -(C₁-C₅)alkyl, -(C₁-C₅)oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

Z is $\begin{array}{c} \text{H} \\ | \\ -\text{C}- \\ | \\ \text{—} \end{array}$ or $\begin{array}{c} \text{—} \\ | \\ \text{N} \end{array}$;

L is -O-, -S-, or -N(R⁶)-;

R⁶ is -H, -(C₁-C₅)alkyl, substituted or unsubstituted aryl(C₁-C₁₀)alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

Y is -CH₂-, -CH₂CH₂-, -CH=CH-, -C(O)CH₂-, -C(O)CH₂CH₂-, -C(O)CH=CH-, -S(O₂)CH₂-, -S(O₂)CH₂CH₂-, -S(O₂)CH=CH-, or -C(O)-; and

W is a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

2. The compound of claim 1 wherein R¹ is tetrazolyl, pyrimidinyl, or pyridinyl.

3. The compound of claim 1 wherein R¹ is -OH, or a salt thereof.

4. The compound of claim 1 wherein R² is unsubstituted aryl or unsubstituted heteroaryl.

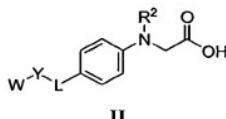
5. The compound of claim 1 wherein R² is substituted aryl and the substitution onto the aryl is unsubstituted -(C₁-C₅)alkyl, -(C₁-C₅)oxyalkyl, or -halo(C₁-C₅)alkyl.

6. The compound of claim 1 wherein R² is $\text{—C}\equiv\text{C—R}^5$ and R⁵ is -(C₁-C₅)alkyl having 0 or 1 heteroatoms.
7. The compound of claim 1 wherein R² is -CH=C(CH₃)₂, -CH₂CH=CH₂.
8. The compound of claim 1 wherein L is -O-, -S-, and Y is -CH₂- ,or -CH₂CH₂-.
9. The compound of claim 1 wherein L is -N(R⁶)- with the proviso that Y may not be -C(O)- where Z is nitrogen and R² is a unsubstituted phenyl.
10. The compound of claim 1 wherein W is substituted or unsubstituted fused aryl bicyclic ring or substituted or unsubstituted fused heteroaryl bicyclic ring.
11. The compound of claim 1 wherein W is a substituted or unsubstituted 5- or 6-membered aryl ring or substituted or unsubstituted 5- or 6-membered heteroaryl ring.
12. The compound of claim 1 or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein
- R¹ is -OH, -NHS(O₂)CH₃, -NH-tetrazole, or tetrazole;
- R² is -(C₂-C₃)alkyl, -NR³R⁴, substituted or unsubstituted phenyl,
-CH=C(CH₃)₂, -CH₂CH=CH₂, or $\text{—C}\equiv\text{C—R}^5$;
- R³ and R⁴ are independently -H, -(C₁-C₅)alkyl, or -(C₁-C₅)oxyalkyl;
- R⁵ is -(C₁-C₅)alkyl, -(C₁-C₅)oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- Z is $\begin{array}{c} \text{H} \\ | \\ \text{—C—} \end{array}$ or $\begin{array}{c} | \\ \text{—N—} \end{array}$;
- L is -O-, -S-, or -N(R⁶)-;
- R⁶ is -H , substituted or unsubstituted aryl(C₁-C₁₀)alkyl or substituted or unsubstituted aryl;
- Y is -CH₂- , -CH₂CH₂- , -CH=CH- , -C(O)CH₂- , -C(O)CH₂CH₂- ,
-C(O)CH=CH- , -S(O₂)CH₂- , -S(O₂)CH₂CH₂- , or -S(O₂)CH=CH- ; and
- W is a substituted or unsubstituted 5- or 6-membered aryl ring or substituted or unsubstituted 5- or 6-membered heteroaryl ring.
13. The compound of claim 12, wherein
- R¹ is -OH;

L is -O-, or -S-; and
Y is -CH₂- , or -CH₂CH₂- .

14. The compound of claim 12, wherein W is a substituted or unsubstituted phenyl.
15. The compound of claim 14, wherein W is substituted with substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted hetero(C₁-C₁₀)alkyl, substituted or unsubstituted halo(C₁-C₁₀)alkyl, substituted or unsubstituted aryl(C₁-C₁₀)alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
16. The compound of claim 2, wherein W is a 5-membered ring selected from the group consisting of
-
- and
- R⁷ is substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted hetero(C₁-C₁₀)alkyl, substituted or unsubstituted halo(C₁-C₁₀)alkyl, substituted or unsubstituted aryl(C₁-C₁₀)alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

17. The compound having the formula (II):



or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein

R² is -H, -(C₂-C₃)alkyl, -NR³R⁴, or substituted or unsubstituted phenyl;

L is -O-, -S-, or -N(R⁶)-;

R⁶ is -H , substituted or unsubstituted aryl(C₁-C₁₀)alkyl or substituted or unsubstituted aryl;

Y is -CH₂- , -CH₂CH₂- , -CH=CH- , -C(O)CH₂- , -C(O)CH₂CH₂- , -C(O)CH=CH- , -S(O₂)CH₂- , -S(O₂)CH₂CH₂- , or -S(O₂)CH=CH- ; and

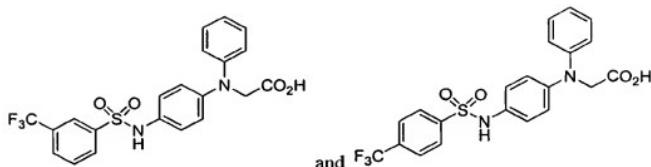
W is a substituted or unsubstituted 5- or 6-membered aryl ring or substituted or unsubstituted 5- or 6-membered heteroaryl ring.

18. The compound of claim 17, wherein

L is -N(R⁶); and

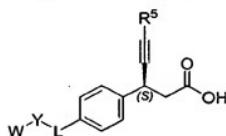
R⁶ is hydrogen.

19. The compound of claim 18 selected from the group consisting of



or a salt thereof.

20. The compound of claim 12 having the formula (III):

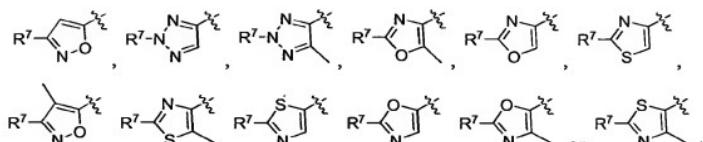


or a pharmaceutically acceptable salt, hydrate or prodrug thereof.

21. The compound of claim 20 wherein R⁵ is methyl.

22. The compound of claim 21 wherein L is -O- or -S- and Y is -CH₂- or -CH₂CH₂-.

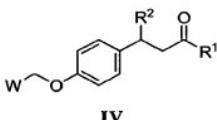
23. The compound of claim 22 wherein W is a 5-membered ring selected from the group consisting of



and

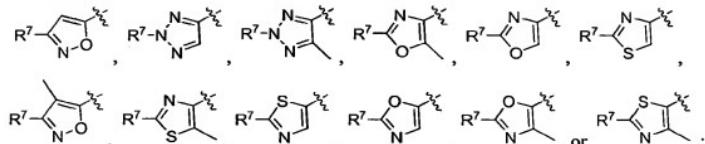
R^7 is substituted or unsubstituted (C_1-C_{10})alkyl, substituted or unsubstituted hetero(C_1-C_{10})alkyl, substituted or unsubstituted halo(C_1-C_{10})alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

24. The compound of claim 23 wherein R^7 is substituted phenyl.
25. The compound of claim 23 wherein R^7 is unsubstituted phenyl
26. The compound of claim 12 having the formula (IV):



or a pharmaceutically acceptable salt, hydrate or prodrug thereof.

27. The compound of claim 26, wherein R^1 is -OH, or a salt thereof.
28. The compound of claim 26, wherein W is substituted phenyl.
29. The compound of claim 28 wherein W is substituted with substituted or unsubstituted (C_1-C_{10})alkyl, substituted or unsubstituted hetero(C_1-C_{10})alkyl, substituted or unsubstituted halo(C_1-C_{10})alkyl, substituted or unsubstituted aryl(C_1-C_{10})alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
30. The compound of claim 26, wherein W is a 5-membered ring selected from the group consisting of

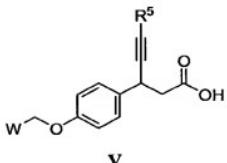


and

R^7 is substituted or unsubstituted (C_1-C_{10})alkyl, substituted or unsubstituted hetero(C_1-C_{10})alkyl, substituted or unsubstituted halo(C_1-C_{10})alkyl, substituted or

unsubstituted aryl(C₁-C₁₀)alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

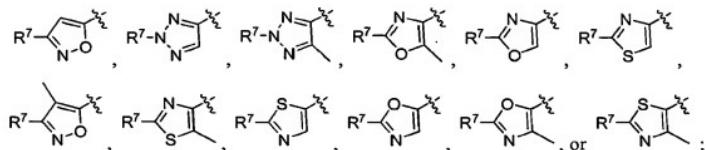
31. The compound of claim 12 having the formula (V):



or a pharmaceutically acceptable salt, hydrate or prodrug thereof.

32. The compound of claim 31 wherein R⁵ is methyl.

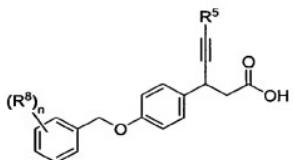
33. The compound of claim 31 wherein W is a 5-membered ring selected from the group consisting of



and

R⁷ is hydrogen, substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted hetero(C₁-C₁₀)alkyl, substituted or unsubstituted halo(C₁-C₁₀)alkyl, substituted or unsubstituted aryl(C₁-C₁₀)alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

34. The compound of claim 31 having the formula (VI):

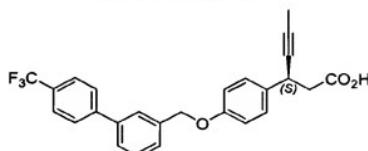


or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein

each R⁸ is independently selected from the group consisting of substituted or unsubstituted (C₁-C₁₀)alkyl, substituted or unsubstituted hetero(C₁-C₁₀)alkyl, substituted or unsubstituted halo(C₁-C₁₀)alkyl, substituted or unsubstituted aryl(C₁-C₁₀)alkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; and

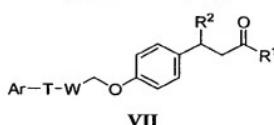
the subscript n is an integer from 0 to 5.

35. The compound of claim 34, wherein the subscript n is 0, 1, or 2.
36. The compound of claim 34, wherein
R⁸ is a methoxy, ethoxy, trihalomethyl, methyl, halo, or cyano group; and
the subscript n is 1 or 2
37. The compound of claim 34, wherein
R⁸ is a phenyl, methoxyphenyl, methylphenyl, trihalomethylphenyl, benzyl, phenoxy, ethoxyphenyl, cyanophenyl, halophenyl, halobenzyl, pyridyl, methoxybenyl, or pyryl group; and
the subscript n is 1 or 2.
38. The compound of claim 36 wherein R⁵ is methyl.
39. The compound of claim 38 wherein the formula is



or a salt thereof.

40. The compound of claim 12 having the formula (VII):



or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein

T is a direct bond, substituted or unsubstituted (C₁-C₅)alkyl or substituted or unsubstituted hetero(C₁-C₅)alkyl; and

Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

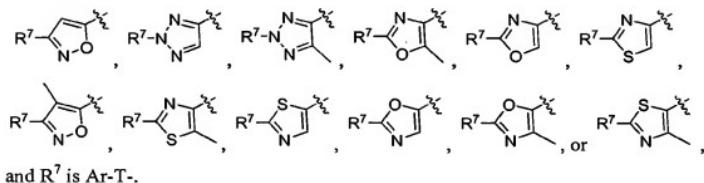
41. The compound of claim 40 wherein R² is -C≡C-CH₃.

42. The compound of claim 41 wherein R¹ is -OH.

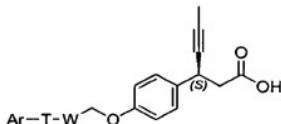
43. The claim 40 or 41 wherein T is a direct bond and Ar is a substituted or unsubstituted benzene ring.

44. The compound of claim 40 or 41 wherein W is phenyl.

45. The compound of claim 40 or 41 wherein W is a 5-membered ring selected from the group consisting of



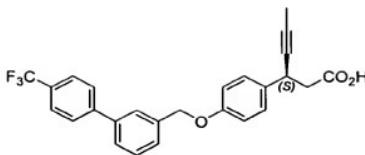
46. The compound of claim 40 having the formula (VIII)



VIII

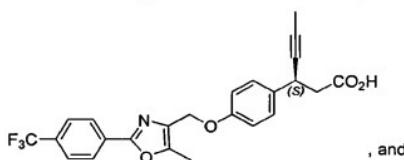
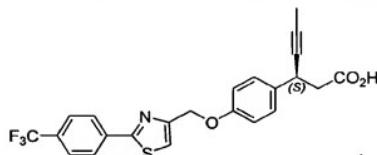
or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein
W, T and Ar are as defined as in claim 40.

47. The compound of claim 46 having the formula:

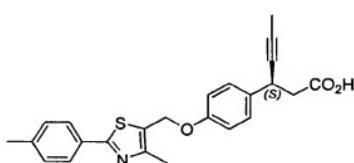


, or a salt thereof.

48. The compound of claim 46 selected from the group consisting of:



, and



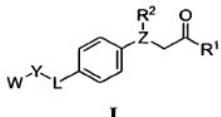
or a salt thereof.

49. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound of any one of claims 1-48.

50. A method for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, cardiovascular disease and atherosclerosis, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-48.

51. The method of claim 50 wherein said disease or condition is type II diabetes.

52. A method for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, cardiovascular disease and atherosclerosis, comprising administering to a subject in need thereof a therapeutically effective amount of a compound having the formula (I):



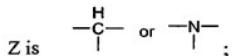
or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein

R¹ is -H, -OH, -NHS(O₂)CH₃, -NH-tetrazole, or tetrazole;

R² is -H, -(C₁-C₈)alkyl, -NR³R⁴, substituted or unsubstituted phenyl, -CH=CR⁹R¹⁰, -CH=CH-R⁹, -CH₂CH=CH₂, -C≡N, or -C≡C-R⁵;

R³ and R⁴ are independently -H, -(C₁-C₅)alkyl, or -(C₁-C₅)oxyalkyl;

R⁵ is -(C₁-C₅)alkyl, -(C₁-C₅)oxyalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;



L is -O-, -S-, or -N(R⁶)-;

R⁶ is -H, substituted or unsubstituted aryl(C₁-C₁₀)alkyl or substituted or unsubstituted aryl;

R⁹ and R¹⁰ are independently selected from group consisting of substituted or unsubstituted (C₁-C₁₀)alkyl or substituted or unsubstituted hetero(C₁-C₁₀)alkyl

Y is -CH₂-, -CH₂CH₂-, -CH=CH-, -C(O)CH₂-, -C(O)CH₂CH₂-, -C(O)CH=CH-, -S(O₂)CH₂-, -S(O₂)CH₂CH₂-, or -S(O₂)CH=CH-, or optionally, -C(O)- unless Z is nitrogen and R² is a unsubstituted benzene ring; and

W is a substituted or unsubstituted 5- or 6-membered aryl ring or substituted or unsubstituted 5- or 6-membered heteroaryl ring.

53. A method for treating a disease or condition responsive to the modulation of GPR40 comprising administering to a subject in need thereof a therapeutically effective amount of a compound of a compound of any one of claims 1-48.

54. The method of claim 53, wherein said disease or condition is selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia and dyslipidemia, cardiovascular disease and atherosclerosis, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-48.

55. A method as in any one of claims 49-54, wherein said compound is administered orally, parentally or topically.

56. A method as in any one of claims 49-54, wherein said compound is administered in combination with a second therapeutic agent.

57. The method of claim 42, wherein said second therapeutic agent is a metformin or a thiazolidinedione.

58. A method for modulating GPR40 function in a cell, comprising contacting a cell with a compound of any one of claims 1-48.

59. A method for modulating GPR40 function comprising contacting GPR40 with a compound of any one of claims 1-48.

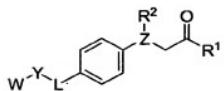
60. A method for modulating circulating insulin concentration in a subject, comprising administering a compound of any one of claims 1-48 to the subject.

61. The method of claim 60, where insulin concentration is increased.

62. The method of claim 60, where insulin concentration is decreased.

ABSTRACT

The present invention provides compounds useful, for example, for modulating insulin levels in a subject and that have the general formula



wherein the definitions of the variables W, Y, L, R¹, and R² are provided herein. The present invention also provides compositions and methods for use of the compounds, for instance, for treatment of type II diabetes.

Figure 1

